GASTROINTESTINAL COMMITTEE

Charles D. Blanke, M.D., Chair
Heniz-Joesf Lenz, M.D., Vice-Chair

Pages: GI 1-71
ABSTRACT

The Gastrointestinal (GI) Committee is a multidisciplinary research team comprised of basic science, translational, and clinical investigators representing a host of disciplines, including Medical, Surgical, and Radiation Oncology, as well as Pathology, Gastroenterology, Diagnostic Imaging, and Biostatistics. The Committee includes expert clinicians and researchers, who specialize in areas including new drug development, clinical trial design, biostatistics, experimental and molecular therapeutics, and molecular pathology. The principal mission of this committee is to develop and vet practice paradigms incorporating clinical and translational medical breakthroughs, ultimately leading to a world-wide reduction in morbidity and mortality from GI malignancies.

Our major accomplishments during the current award period include: (1) Coordination and completion of 7 phase III GI Intergroup trials, involving a variety of upper and lower GI sites, with potential to change existing standard of care therapies. (2) The conceptualization, design and analysis of 12 innovative pilot phase I and II trials for GI cancers, examining novel single agents, combinations, and targeted therapeutics. (3) Complete reorganization of the committee’s structure, to augment its multidisciplinary approach to GI malignancy research. (4) Systematic mentoring of young investigators, leading to effective training of the next generation of GI cancer researchers. (5) Widespread placement of GI Committee members in NCI-based national leadership positions. (6) Extensive collaboration with other SWOG committees and other Cooperative Groups, to more rapidly and fully answer important national questions in GI malignancy research and care. (7) Development of new technologies and identification of new molecular markers associated with outcome in GI malignancies, with incorporation of correlative sub-studies into the majority of GI Committee trials.

Our scientific plans for the next grant period are to: (1) Develop clinical-translational trials that address significant questions in GI oncology and which possess the potential to alter the standard of care for patients. (2) Translate basic science knowledge concerning the molecular and biochemical basis of GI neoplasms into the identification of new targets for therapeutic intervention. (3) Incorporate correlative projects into all major GI Committee trials, collecting patient samples and contributing to basic science knowledge. (4) Contribute as both a leader and active participant in GI Intergroup efforts. (5) Collaborate with the SWOG Prevention Committee in large-scale phase III trials aimed at delaying or halting development of GI cancers.
MEMBERSHIP

COMMITTEE LEADERSHIP
Chair: Charles D. Blanke, M.D.
Vice-Chair: Heinz-Josef Lenz, M.D.
Executive Officer: Bruce Redman, D.O.
Statistician: Jacqueline Benedetti, Ph.D.

SCIENTIFIC LEADERSHIP
Translational Medicine
Translational science: Heinz-Josef Lenz, M.D.
Christopher L. Corless, M.D., Ph.D.

Early Therapeutics: Ramesh Ramanathan, M.D.
Robert P. Whitehead, M.D.

Radiation Oncologist: Lisa A. Kachnic, M.D.
Surgical Oncologists: Kevin G. Billingsley, M.D.
Scott A. Hundahl, M.D.
Andrew M. Lowy, M.D.
Syed A. Ahmad, M.D.

Gastroesophageal: Syma Iqbal, M.D.
Lawrence P. Leichman, M.D.
Pancreatic: Philip A. Philip, M.D., Ph.D.
Hepatobiliary: Anthony B. El-Khoueiry, M.D.
Melanie Thomas, M.D.
Colorectal: Philip J. Gold, M.D.
Anthony F. Shields, M.D., Ph.D.

DESIGNATES
Clinical Research Associate: Michelle King, R.H.I.A.
Control/Prevention Liaison: Christine McLeod
Data Coordinator: Stephanie Edwards
Rodney Sutter
Nurse: Rita A. Kaul, R.N., B.S.N.
Valerie A. Parks, R.N.
Pathologist: Christopher L. Corless, M.D., Ph.D.
Patient Advocates: Erin Stennis (Colon)
Porsha James (Pancreatic)
Protocol Coordinator: Gretchen E. Goetz
Statisticians: Bryan Goldman, M.S.
Cathryn Rankin, M.S.

Organization of the Committee
The GI Committee is a scientific, disease-oriented group with a defined research agenda directed at establishing effective prevention and treatment paradigms for malignancies involving the GI tract. The panoply of GI neoplasms includes a large number of distinct cancers, which may or may not share underlying biologic similarities, but which certainly differ in terms of chemo-sensitivity and surgical approach to limited disease. To ascertain treatment and research approaches for each type of malignancy are organized in a multi-disciplinary fashion, the GI Committee was completely restructured during this grant cycle. Five subcommittees representing anatomic GI sites were established, with each run by one or two Medical Oncology co-chairs, as well as a Surgical Liaison (essentially a surgical co-
chair). These subcommittees comprise Gastroesophageal Cancer (Syma Iqbal, Lawrence Leichman, and Scott Hundahl), Pancreatic Cancer (Philip Philip, and Andrew Lowy), Hepatobiliary Cancer (Melanie Thomas, Anthony El-Khoueiry, and Syed Ahmad, and Colorectal Cancer (Philip Gold, Tony Shields, and Kevin Billingsley). To ensure continuity across subcommittees and to harness expertise that can be broadly applied, Translational Medicine (Heinz Lenz, and Christopher Corless) and Drug Development (Ramesh Ramanathan and Robert Whitehead) Subcommittees were named as distinct entities. Lisa Kachnic was appointed Radiation Oncology Liaison to the entire GI Committee, and as such she helps voice RT-related questions, as well as to integrate RT techniques into multimodality protocols. Subcommittee chairs and liaisons also serve as members of the GI Core Committee, which is responsible for guiding the research path of the overall committee, and which decides how to best participate in Intergroup efforts.

Recognizing that twice per year meetings were not sufficient to keep pace with the rapid advancement in GI oncology knowledge, scheduled monthly teleconferences were established by GI Committee leadership. These meetings are used to discuss specific clinical and translational research goals, to generate and prioritize new protocols, to track basic science information that might be germane to translational protocols, and to monitor accrual to existing studies. Additional, more specialized teleconferences are called by individual subcommittees as needed.

Below is an overview of the GI committee membership by specialty:

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### TREATMENT PROTOCOLS ACTIVE DURING REPORT PERIOD

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*Registrations are through 12/31/2008*
RELEVANT PAST, CURRENT AND FUTURE STUDIES LED BY SWOG

PAST STUDIES

S0030: Phase II Protocol for Assessment of Capecitabine for Advanced Colorectal Cancer in Patients Aged 70 Years and Older

S0033: Phase III Randomized, Intergroup Trial Assessing the Clinical Activity of STI-571 at Two Dose Levels in Patients with Unresectable or Metastatic Gastrointestinal Stromal Tumors (GIST) Expressing the KIT Receptor Tyrosine Kinase (CD117)

S0107: A Phase II Trial of Epothilone B Analogue BMS-247550 (NSC #710428) Every 21 Days in Patients with Advanced Pancreas Cancer

S0127: A Phase II Study of OSI-774 (NSC #718781) in Unresectable or Metastatic Adenocarcinoma of the Stomach and Gastroesophageal Junction

S0202: A Phase II Trial of Gemcitabine and Capecitabine in Patients with Unresectable or Metastatic Gallbladder Cancer or Cholangiocarcinoma

S0205: A Phase III Randomized, Open-Label Study Comparing Gemcitabine Plus Cetuximab (IMC-225) Versus Gemcitabine as First-Line Therapy of Patients with Advanced Pancreas Cancer

S0302: A Phase II Feasibility Translational Research Trial of Induction Chemotherapy Followed by Concomitant Chemoradiation in Patients with Clinical T3-T4 Rectal Cancer

S0303: A Phase II Trial of Modified FOLFOX6 versus CAPOX, With Bevacizumab (NSC-704865) or Placebo, as First-Line Therapy in Patients with Previously Untreated Advanced Colorectal Cancer

S0304: A Phase II Feasibility Translational Research Trial of Induction Chemotherapy Followed by Concomitant Chemoradiation in Patients with Clinical T3-T4 Rectal Cancer

S0336: A Phase II Trial of Depsipeptide (NSC-630176) in Colorectal Cancer Patients Who Have Received Either One or Two Prior Chemotherapy Regimens for Metastatic or Locally Advanced, Unresectable Disease

S0356: Phase II Study of Oxaliplatin Plus Protracted Infusion 5-Fluorouracil and Radiation for Potentially Curable Esophageal Cancer

S0413: A Phase II Study of GW572016 (NSC-727989) as First Line Therapy in Patients with Advanced or Metastatic Gastric Cancer

S0414: Cetuximab plus Cisplatin, Irinotecan, and Thoracic Radiotherapy for Locally-Advanced, Non-Metastatic, Clinically Unresectable Esophageal Cancer: A Phase II Trial with Molecular Correlates

S0415 – Phase II Trial of Cetuximab as Second Line Therapy in Metastatic Esophageal Cancer

S0425: Neoadjuvant Chemoradiation Therapy with Oxaliplatin and Capecitabine for Patients with Surgically Resectable Gastric Cancer: A Pilot Phase II with Molecular Correlates

S0514: A Phase II Study of Sorafenib as a Single Agent in Patients with Unresectable or Metastatic Gallbladder Cancer or Cholangiocarcinoma

CURRENT STUDIES

S0502: Phase III Trial of Imatinib Mesylate, plus or minus Bevacizumab, in Patients with Incurable...
Gastrointestinal Stromal Tumors

**S0518**: Phase III Prospective Randomized Comparison of Depot Octreotide Plus Interferon Alpha versus Depot Octreotide plus Bevacizumab (NSC #704865) in Advanced, Poor Prognosis Carcinoid Patients

**C80405**: A Phase III Trial of Irinotecan/5-FU/Leucovorin or Oxaliplatin/5-FU/Leucovorin with Bevacizumab, or Cetuximab (C225), or with the Combination of Bevacizumab and Cetuximab for Patients with Untreated Metastatic Adenocarcinoma of the Colon or Rectum

**S0600**: Phase III Trial of Irinotecan-Based Chemotherapy plus Cetuximab (NSC-714692) with or without Bevacizumab (NSC-704865) as Second-line Therapy for Patients with Metastatic Colorectal Cancer who have Progressed on Bevacizumab with either FOLFOX, OPTIMOX or XELOX plus Bevacizumab

**S0727**: A Phase I and Randomized Phase II Trial of Gemcitabine + Erlotinib (NSC-71817 + IMC-A12 (NSC-742460) vs. Gemcitabine + Erlotinib as First Line Treatment in Patients with Metastatic Pancreatic Cancer

**FUTURE (LATE-STAGE PLANNING ONLY) STUDIES**

**S0713**: A Phase II Study of Oxaliplatin and Capecitabine in Combination with Cetuximab and Radiation in Pre-Operative Therapy of Rectal Cancer

**S0809**: A Phase II Trial of Adjuvant Capecitabine/Gemcitabine Chemotherapy Followed by Concurrent Capecitabine and Radiotherapy in Extrahepatic Cholangiocarcinoma

**S09-TBD**: A Phase II Study of Sorafenib in Combination with Erlotinib in Patients with Unresectable or Metastatic Gallbladder Carcinoma and Cholangiocarcinoma

**S0205A**: Predictive and Prognostic Value of Tumor K-Ras Mutation Status, Amphiregulin and Epiregulin and Gene Expression Levels and Germ-line Polymorphisms Involved in the EGFR and Gemcitabine Pathway in Advanced Pancreas Cancer: A Study of Tissues from SWOG Protocol 0205

R0848, Gemcitabine, With and Without Erlotinib, Followed by a Second Randomization with and without Chemoradiation, as Adjuvant Treatment for Pancreatic Head Cancer: A Phase III RTOG/SWOG/NCIC/EORTC Study

**S0916**: A Phase II Trial of Cetuximab and Dasatinib as Second-Line Therapy in Patients with Metastatic Esophageal Cancer

**S0918**: A Phase Ib/II Study of Gemcitabine, Erlotinib, and AMG102 in Patients with Nonmetastatic, Locally Advanced, Pancreatic Adenocarcinoma

**S09-TBD**: A Phase I/II Clinical Trial of Modified FOLFOX and Everolimus in Patients with Metastatic Pancreatic Cancer

**C80702**: A Phase III Trial of FOLFOX +/- Celecoxib, Administered for 3 or 6 Months, in Patients with Fully-Resected Stage III or High-Risk Stage II Colon Cancer

**S09-TBD**: A Phase II Study Prospectively Randomizing Patients Based on Markers, TS and ERCC1 for Advanced/Metastatic Gastric Cancer or Gastroesophageal Junction (GE) Junction Cancer

**S09-TBD**: A Phase II Study Prospectively Randomizing Patients Based on Markers, TS and ERCC1 for Advanced/Metastatic Colorectal Cancer
DESCRIPTION OF TRIALS: PAST STUDIES

**SWOG 0030:** Phase II Protocol for Assessment of Capecitabine for Advanced Colorectal Cancer in Patients Aged 70 Years and Older (Activated: 2/1/2003; Permanently Closed: 2/1/2005)

**Schema**
None available

**Rationale**
Cancer in patients aged 70 and older collectively represents one of the rapidly increasing demographic groups with malignancy. One of the issues most poorly characterized is the specific pharmacology and efficacy of chemotherapy in patients aged 70 and older. For patients with significant co-morbidities, capecitabine has been approved by the FDA for first line therapy. Thus, the goal of this study was to determine the anticancer efficacy and toxicity of capecitabine in this patient population and to characterize the genetic and genomic profile of this patient population relative to clinical outcome.

**Objectives**
- To assess the feasibility of enrolling patients aged 70 years and older with advanced colorectal cancer to a structured Phase II trial including pharmacokinetic sampling.
- To assess the anticancer efficacy of capecitabine for the management of advanced colorectal cancer in patients aged 70 years and older based on objective response rate (confirmed and unconfirmed complete and partial responses) and two-year survival.
- To estimate the toxicity and tolerability of the regimen in this specific population group.
- To assess the feasibility of using standardized self-report measures of co-morbidity, depression and functional status in an elderly population of patients with cancer.
- To assess parameters of clinical pharmacology of capecitabine in patients aged 70 years and older, including half life value(s), AUC and steady state levels.
- To assess whether patients under 60 years have clinical pharmacologic parameters similar to those reported in the literature (to validate our assay system).
- To explore, at a preliminary level, the feasibility of studying genetic polymorphisms and gene expression levels of enzymes involved in drug metabolism and resistance to capecitabine (including thymidylate synthase [TS], dihydropyrimidine dehydrogenase [DPD] and thymidylate phosphorylase) in these population groups.

**Statistical Endpoints**
The primary objective was to determine the feasibility of accruing patients with advanced colorectal cancer who are 70 and older. Accrual of 3 patients per month in the age 70 and older group would allow for a reasonable phase II program. Objectives specific to capecitabine were to estimate baseline co-morbidity and pk parameters, response, two-year survival and toxicity probabilities in the patients aged 70 and older. Of particular interest is the tolerability of this regimen as evidenced by early discontinuation of treatment due to reasons other than disease progression. The regimen would be judged sufficiently tolerable for use in the elderly if \( \leq 17 \) of 60 discontinue treatment early. PK estimates for those over 70 would also be assessed against the literature. A comparator group of patients < 60 was accrued as well.

**Results and Conclusions:**
This study was closed on February 1, 2005 due to poor accrual and the changing standard of care in the community. Twenty-six patients were assessable for toxicities. One Grade 4 cardiac infarction was
observed in the age ≥ 70 years group. No other Grade 4 or 5 toxicities have been observed. In the ≥ 70 group, five confirmed partial responses, one unconfirmed complete response and two unconfirmed partial responses were observed for an overall response probability of 42% (95% confidence interval of 20% to 67%). No responses were observed in the age less than 60 group. Preliminary pk analysis suggests a difference for capecitabine in the elderly versus patients <65 years of age (manuscript in preparation).

**SWOG-0033:** Phase III Randomized, Intergroup Trial Assessing the Clinical Activity of STI-571 at Two Dose Levels in Patients with Unresectable or Metastatic Gastrointestinal Stromal Tumors (GIST) Expressing the KIT Receptor Tyrosine Kinase (CD117) (Activated: 12/15/00; Permanently Closed: 9/01/01)

**Schema**

Unresectable or metastatic GIST with documented KIT expression by DAKO anti-CD117 IHC

Randomization

Arm 1
Low Dose STI-571

Progression

Crossover Registration

High Dose STI-571

Progression

Arm 2
High Dose STI-571

Progression

Off Protocol Treatment
Off Protocol Treatment

**Rationale**
GISTs, the most common mesenchymal tumors of the GI tract arise from the interstitial cells of Cajal. In vivo evidence suggests their malignant behaviour is often driven by constitutive mutations in *KIT*. Imatinib mesylate inhibits the KIT RTK at an IC50 of approximately 100 nM, and exposure of a primary GIST cell line showed that these cells appear to be strongly dependent upon the activity of the mutant receptor to prevent apoptosis. A phase II trial of imatinib in patients with incurable GIST demonstrated a response rate of at least 50%, with an acceptable toxicity profile.\(^1\,^2\) That trial tested two doses of imatinib in randomized phase II fashion, but it was not powered to show superiority for either dose.

**Objectives**
- To compare overall and progression-free survival for patients with unresectable or metastatic gastrointestinal stromal tumors (GIST) expressing KIT (CD 117) treated with low dose STI-571 versus high dose STI-571.
- To assess response rates (confirmed, unconfirmed, complete and partial) of patients treated with these two doses of STI-571.
- To assess toxicities of patients treated with these two doses of STI-571.
- To obtain tissue and blood samples from GIST patients before and following treatment with STI-571 for future correlative studies.

**Statistical Endpoints**
The primary objective of this study was to compare the survival of patients with incurable malignant GIST treated with high dose imatinib (800 mg/day) versus lower dose drug (400 mg/day). It was postulated that GIST patients treated with imatinib at 400 mg/day would have an 18 month median survival. This trial had a .85 power to detect a 40% increase in median survival, using a two-sided test with a .05 significance level. If median progression-free survival were 12 months, then 600 patients would also have .92 power to detect a 40% increase in median progression-free survival. Assuming that 80% of patients have measurable disease, a sample size of 250 patients per arm would be sufficient to estimate response rates to within at worst ± 6% (95% confidence interval).

**Results and Conclusions**
This landmark phase III trial was conceived and initiated by the ICAS Subcommittee of SWOG, with accrual completed prior to this grant cycle. However, final analysis, much of the correlative work, and publication were conducted by the GI Committee during this current funding period. Successor GIST studies (including the ongoing phase III front-line trial) are being conducted by the GI group. 746 patients were enrolled onto S0033 in 9 months. With a median follow-up of 4.5 years, median progression-free survival was 18 months for patients on the standard-dose arm, versus 20 months for those receiving higher-dose imatinib. Median overall survival was 55 and 51 months, respectively. There were no statistically significant differences in objective response rates, progression-free survival, or overall survival. After progression on 400 mg/day, 33% of patients who crossed over to the high-dose imatinib regimen achieved either an objective response or stable disease. These results were recently published (Blanke et al., J Clin Oncol 26(4):626-32, 2008). S0033 confirmed the effectiveness of imatinib as primary systemic therapy for patients with incurable GIST but did not show any advantage to higher dose treatment. It also showed benefit for escalating the imatinib after progression was seen, establishing this strategy as standard of care for front-line patients failing imatinib. Additionally on S0033, Important correlative work was conducted by the GI Correlative subcommittee co-Chair Dr. Christopher Corless, in conjunction with Michael Heinrich (Heinrich et al. J Clin Oncol 26:5360-5367, 2008). This will be described further in this chapter.
SWOG S0107: A Phase II Trial of Epothilone B Analogue BMS-247550 (NSC #710428) Every 21 Days in Patients with Advanced Pancreas Cancer (Activated 7/1/2001; Permanently Closed 6/1/2003)

Schema
None available

Rationale
BMS-247550 is a semi-synthetic analogue of the natural product epothilone B with a mode of action similar to the taxanes, microtubular stabilization. However it is effective in in vitro and in vivo animal models in which the tumor is resistant to paclitaxel. BMS-247550 has broad spectrum antitumor activity in preclinical human tumor models in nude mice, including paclitaxel-sensitive and resistant cell lines.

Objectives
- To assess the six month survival rate in patients with advanced adenocarcinoma of the pancreas treated with BMS-247550.
- To assess the time to treatment failure in this group of patients.
- To assess the frequency and severity of toxicities associated with this therapy.
- To assess confirmed response (complete and partial) as a secondary endpoint in those patients with measurable disease.
- To study the pharmacokinetic profile of BMS-247550 in patients with advanced pancreatic cancer.
- To study the effect of BMS-247550 on gene expression in peripheral blood mononuclear cells isolated from patients with advanced pancreatic cancer undergoing therapy with BMS-247550.

Statistical Endpoints
The primary goal of this study was to evaluate the six month overall survival rate in patients with pancreatic cancer treated with BMS-247550. It was assumed that BMS-247550 would not be of further interest if the true 6 month survival rate were 35% or less, but of considerable interest if it were 55% or more. A two-stage design was used. 39 patients were sufficient to estimate the true confirmed response rate to within ± 16% and 55 patients were sufficient to estimate the 6-month treatment failure rate and probability of a particular toxicity to within ± 13%.

Results and Conclusions
Sixty eligible patients were registered. The estimated 6-month survival was 60% (95% CI 48%-72%) with a median survival of 7.2 months and an estimated time to treatment failure of 2.3 months. The confirmed response probability was 9% (95% CI 3%-20%) and unconfirmed partial response rate was 21% (96% CI 12%-34%). Common toxicities were neutropenia/granulocytopenia, nausea and vomiting, and neuropathy. There was one death, whose cause was not determined but which was judged “possibly” related to treatment. It was concluded that BMS-247550 showed at best modest activity in patients with advanced pancreas cancer.

S0127 A Phase II Study of OSI-774 (NSC #718781) in Unresectable or Metastatic Adenocarcinoma of the Stomach and Gastroesophageal Junction (Activated 6/02; Closed 8/15/03)

Schema
OSI-774 150 mg by mouth daily 1-28; no breaks between cycles

Rationale
The median survival for patients with metastatic gastric and gastroesophageal (GE) junction adenocarcinoma is only 6-8 months. The Southwest Oncology Group Gastrointestinal Correlative Sciences Subcommittee and other laboratories had shown that the epidermal growth factor receptor (EGFR) and its naturally occurring ligand TGF-alpha are frequently over-expressed in gastric adenocarcinomas. OSI-774 is an oral EGFR tyrosine kinase inhibitor that had demonstrated anti-tumor activity in preclinical models and Phase I clinical trials.
Objectives
- Primary: To assess the overall response rate (confirmed complete and partial responses) to OSI-774 in two different patient strata, those with advanced gastric adenocarcinoma and those with GE junction adenocarcinoma.
- To assess the frequency and severity of toxicities associated with this treatment.
- To evaluate overall survival and time to treatment failure in patients with gastric and GE junction adenocarcinomas treated with OSI-774.
- To explore in a preliminary fashion the value of intratumoral expression of epidermal growth factor receptor (EGFR) in predicting response to OSI-774.
- To explore the feasibility of determining the effect of OSI-774 on EGFR tyrosine kinase and other downstream targets in a limited number of pre- and post-treatment biopsies

Statistical Endpoints
This study was designed to have a two-stage design, conducted separately in two strata: patients with cancers of the gastroesophageal junction, and patients with cancer of the stomach. In each stratum, it was assumed that this therapy will be of no further interest if the true response probability is 5% or less, but would warrant further study if the true probability is 20% or more. Twenty patients were to be registered (in each stratum) to the first stage of accrual. If at least one response is observed, that stratum would accrue an additional 20 patients. Five or more responses out of a total of 40 eligible patients in a single stratum would be evidence suggesting that the regimen will be of further interest.

Results and Conclusions
The gastric stratum closed after the first stage of accrual, having failed to meet the protocol specified goals. The gastroesophageal stratum completed accrual to the second stage. In total, sixty-eight patients were eligible for analysis. Common toxicities seen included skin rash, fatigue, and AST/ALT elevation. There was been one confirmed complete response, three confirmed partial responses (PRs) and one unconfirmed PR for an overall confirmed response probability of 9% (95% CI, 3% to 22%), all occurring in the GEJ stratum. No responses were observed in the ST stratum. The median survival was 6.7 months in GEJ and 3.5 months in ST stratum. Neither intratumoral EGFR, transforming growth factor–alpha or phosphorylated Akt kinase expression nor plasma proteomic analyses were predictive of clinical outcome. No somatic mutations of the EGFR exons 18, 19, or 21 were detected and there was no gross amplification of EGFR by fluorescence in situ hybridization. It was concluded that erlotinib is active in patients with GEJ adenocarcinomas, but appears inactive in gastric cancers. The molecular markers examined did not suggest a correlation with response.

SWOG-0202: A Phase II Trial of Gemcitabine and Capecitabine in Patients with Unresectable or Metastatic Gallbladder Cancer or Cholangiocarcinoma (Activated: 9/1/03; closed to patient entry: 4/1/05)

Schema
Single arm: Gemcitabine 1000 mg/m2 IV over 100 min, D1 and D8, every 21 days
Capecitabine 650 mg/m2 PO BID X 14 days, every 21 days

Rationale
5-Fluorouracil, alone or in combination, represented the only therapeutic option for patients with unresectable or metastatic gallbladder carcinoma and cholangiocarcinoma. Given the poor outcomes in this disease, this study was designed to evaluate the efficacy of the combination of gemcitabine and capecitabine based on the preliminary efficacy results of the combination in patients with pancreatic cancer, the common embryologic origin of the exocrine pancreas and gallbladder, and the preliminary efficacy of single agent gemcitabine in gallbladder and biliary cancers.

Objectives
- To assess the response rate of gemcitabine and capecitabine in patients with gallbladder
carcinoma and cholangiocarcinoma

- To assess overall survival
- To assess qualitative and quantitative toxicities of this regimen
- To assess the feasibility of accruing patients with this disease site
- To evaluate in a preliminary fashion relevant prognostic markers in gallbladder and cholangiocarcinoma

**Statistical Endpoints**

Since SWOG had not conducted a study in this disease site in recent years, one of the goals was to determine the feasibility of studying this disease site in the cooperative group setting. The plan was to close the study if the accrual average was less than 1 patient per month. It was assumed that the gemcitabine and capecitabine combination would not be of further interest if the true response rate was <5%, but of considerable interest if it were ≥20%. A two-stage design was used. With a planned accrual of 40 patients, the design had a significance level of 0.047 and a power of 0.92.

**Results and Conclusions**

The study accrued 52 evaluable patients from September 2003 until April 2005. Six experienced grade 4 toxicities: 1 thrombosis/embolism and muscle pain, 1 fatigue and 4 neutropenia, 1 of whom also had grade 4 leukopenia and grade 4 anemia. There were 7 confirmed partial responses for a confirmed response probability of 13% (95% CI 6% to 26%). Five patients had an unconfirmed partial response for an overall response probability of 24% (95% CI 13% to 38%). Additionally, fourteen patients (27%) stable disease. The 6-month overall survival was 55% (95% CI 42%-70%) and median survival was 7.0 months.

Exploratory correlative studies were performed on 22 patient samples and included the evaluation of polymorphisms in the thymidilate synthase (TS) 5’ and 3’ terminals, the MTHFR gene, and cytidine deaminase. The small number of patient samples evaluated did limit the statistical value of any potential correlations with clinical outcome but provided hypothesis generating observations and proved the feasibility of performing correlative studies on patient samples in this disease. Based on results from this study, SWOG elected to pursue targeted agents, rather than chemotherapeutic agents, in future trials.

Schema:

Histologically or cytologically confirmed diagnosis of adenocarcinoma of pancreas that is not amenable to curative surgical resection or is distantly metastatic

Randomization and stratification

(Stratified by: disease status [locally advanced unresectable vs. metastatic], Zubrod Performance Status [0 or 1 vs. 2] and prior pancreatectomy [yes vs. no])

Arm 1

Gemcitabine + Cetuximab

Arm 2

Gemcitabine

Rationale
Epidermal growth factor receptor (EGFR) activation is frequent in pancreatic adenocarcinoma. Preclinical evidence supports the targeting of EGFR to increase gemcitabine-induced apoptosis and to inhibit angiogenesis. A pilot phase II trial by SWOG investigators demonstrated an improvement in survival at one year in patients with advanced pancreas cancer treated with gemcitabine plus cetuximab.⁴

Objectives
- To compare overall survival in advanced pancreatic cancer patients treated with gemcitabine with or without cetuximab.
- Time to treatment failure
- Objective response rates
- Patient-reported outcomes
- Determination of EGFR expression by immunohistochemistry, as well as other correlative work (see section XXX)

Statistical Endpoints
The cetuximab (experimental) arm would be deemed superior to gemcitabine alone if the median survival increased from 6 months to 8 months, corresponding to a hazard ratio of 1.33. A comparison of overall survival in the subset of patients who were EGFR positive was also to be performed. 704 eligible patients will be sufficient to detect a 1.33 hazard ratio with 92% power, based on a one-sided 0.0125 test. The
final analysis was based on a stratified log rank test, with a 1-sided level of .0105 to Overall survival was
the primary endpoint, and will be evaluated primarily by the stratified log rank test, with stratification
factors. Time-to-treatment failure (TTF) and response were secondary endpoints to be analyzed by the
stratified log rank test in the same manner as for the overall survival analysis. The response rates
between the two treatment arms were compared using logistic regression, with adjustment for the
stratification factors.

Results and Conclusions
S0205 was activated in January of 2004 and completed accrual in April 2006, at almost twice the
projected accrual rate. Seven hundred and sixty-six patients were enrolled on the study, 87% with PS
0/1, and 22% with locally advanced disease. Median survival of gemcitabine and gemcitabine plus
cetuximab were 5.9 months and 6.4 months, respectively (hazard ratio, 1.09, p = 0.14). PFS and ORR
were similar though TTF was 1.8 and 2.5 months in the gemcitabine versus gemcitabine plus cetuximab
arms (p 0.0014). Toxicities were similar in the two arms of the study except for rash that was more
frequent in the cetuximab arm. It was concluded that gemcitabine plus cetuximab did not improve patient
outcome in an unselected pancreatic cancer population. Correlative work is ongoing.
SWOG 0303: A Phase III Trial of Modified FOLFOX6 versus CAPOX, With Bevacizumab (NSC-704865) or Placebo, as First-Line Therapy in Patients with Previously Untreated Advanced Colorectal Cancer (Activated: 4/1/2004; Closed: 9/1/2004)

Schema

Histologically or cytologically confirmed diagnosis of locally advanced, recurrent or metastatic colorectal adenocarcinoma that is not curable by surgery or amenable to radiation therapy with curative intent.

Randomization

- mFOLFOX6:
  - Oxaliplatin
  - Leucovorin
  - 5-Fluorouracil
- CAPOX:
  - Oxaliplatin
  - Capecitabine

+ +

Bevacizumab or Placebo*  Bevacizumab or Placebo*

Rationale

Intergroup N9741 established FOLFOX4 as one standard of care option in treatment of patients with advanced colorectal cancer. However, the scheduling of drug was inconvenient and use of infusional 5-FU required minor surgery. Trials substituting oral fluoropyrimidines reported similar efficacy results. This study intended to compare an IV 5-FU-containing regimen with oxaliplatin (modified FOLFOX6), to a regimen using capecitabine with the platinum. Additionally, while bevacizumab significantly improved the efficacy of bolus IFL, the median survival for the combination arm was 20.3 months, a figure very similar to that seen with FOLFOX4 alone on N9741 (19.5 months). This was to be the first Intergroup trial testing that drug, with oxaliplatin, in an untreated population.

Objectives

- To compare overall survival in patients with colorectal cancer treated with 5-fluorouracil, leucovorin and oxaliplatin (mFOLFOX6) versus capecitabine and oxaliplatin (CAPOX)
- To compare overall survival in patients treated with mFOLFOX6 or CAPOX, with and without the addition of bevacizumab
- To compare progression-free survival and time to treatment failure between these treatment arms
- To compare response (among patients with measurable disease) between these treatment arms
- To compare the toxicity rates between the mFOLFOX6- and CAPOX-containing treatment regimens
- To assess patient report of functional status and convenience of therapy.
- To evaluate germ-line polymorphisms of DNA repair (such as ERCC-1, XRCC1, GST-P1, XPD, ribonucleotide reductase), target (thymidylate synthase, dihydropyrimidine dehydrogenase, thymidine phosphorylase) enzymes, angiogenesis (e.g. vascular endothelial growth factor [VEGF]) and growth factors (e.g. the epithelial growth factor receptor [EGFR]) as potential predictors of survival and progression-free survival, as well as toxicity from chemotherapy.
Statistical Endpoints
The primary objective was to compare overall survival in patients with colorectal cancer treated with 5-fluorouracil/leucovorin and oxaliplatin versus those treated with capecitabine and oxaliplatin, and to compare survival among patients treated with these two regimens to the same regimens plus bevacizumab. This study was designed as a 2 X 2 factorial design. If there was no treatment interaction between the chemotherapy question and the bevacizumab question, the arms would be combined to test the main effects. 2200 eligible patients, this would be sufficient to rule out a 1.18 or greater hazard ratio for the intravenous versus oral fluoropyrimidine comparison with 91% power, based on a one-sided 0.025 alpha level, and 95% power to detect a 1.20 hazard ratio for improved survival on the bevacizumab containing regimens.

Results and Conclusions
This study was closed on September 1, 2004 resulting from planned early analysis of E3200 (second-line study of bevacizumab in colorectal cancer patients) by the principle investigators, with the subsequent emergence of bevacizumab as standard of care. The oral versus IV fluoropyrimidine question was not sufficiently interesting alone to maintain the study. Thirty-three patients were accrued.

SWOG 0304: A Phase II Feasibility Translational Research Trial of Induction Chemotherapy Followed by Concomitant Chemoradiation in Patients with Clinical T3-T4 Rectal Cancer (Activated: 8/1/2004; Permanently Closed: 2/1/2006)

Schema

Rationale
This study would be the first North American cooperative group effort to prospectively assess the feasibility of obtaining intratumoral molecular markers thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD), and excision repair cross complementing gene-1 (ERCC-1) in patients receiving combined-modality therapy for rectal cancer. Furthermore, the intention was to assess the objective response rate and toxicity of 5-FU-based and non-5-FU-based chemotherapy in patients with locally advanced rectal adenocarcinoma who exhibit pre-treatment intratumoral molecular marker profiles not predicting resistance to fluorinated pyrimidine-based chemotherapy. This study would also establish as a potential standard a baseline Southwest Oncology Group experience with a widely used combined-modality regimen, though untested in the cooperative group setting, of capecitabine and pelvic radiotherapy.

Objectives
- To assess the feasibility of obtaining a pre-treatment determination of intratumoral molecular markers TS, DPD and ERCC-1 for use in selection of the appropriate regimen for induction cytotoxic combination chemotherapy.
- To assess the response rate (confirmed plus unconfirmed, complete and partial) among cT3-cT4 rectal adenocarcinoma patients treated using a targeted approach.
- To assess the toxicity of induction cytotoxic chemotherapy and subsequent chemoradiation in cT3-cT4 rectal adenocarcinoma.
Statistical Endpoints
This study was to include two parts to address the feasibility question. The first was to assess the ability to establish a good link to institution pathologists to obtain rapid submission of required specimens. Accrual was to be limited to 2 or 3 institutions, the percentage of patients for whom specimen submission is accomplished within a week of registration was monitored. Receipt of 8 or more specimens within a week from 10 registered patients would be sufficient to open the trial to additional institutions. For the second step of accrual, 50 eligible patients accrued were necessary in order to estimate the feasibility rate to within +/-14%. Assuming that 15% of patients are not able to have their molecular analysis results performed in a timely manner (within 3 weeks of a given biopsy), 65 total patients will need to be accrued to yield 50 eligible and analyzable patients.

Results and Conclusions:
The study was closed on February 1, 2006 having accrued no patients. Although there was significant interest in this design, it was felt that the population chosen was not ideal, being relatively modest in number versus other stages of rectal cancer. It did highlight the importance of simplifying correlative studies, demonstrating some are simply too complex and cumbersome to be practical in a cooperative group setting.

SWOG 0336: A Phase II Trial of Depsipeptide (NSC-630176) in Colorectal Cancer Patients Who Have Received Either One or Two Prior Chemotherapy Regimens for Metastatic or Locally Advanced, Unresectable Disease. (Activated 4/15/2004; Permanently Closed 9/1/2005.)

Schema
None available

Rationale
Approximately 60% of colorectal cancers have ras gene mutations. Depsipeptide (a product of Chromobacterium violaceum) is able to induce reversion of the ras transformed phenotype to normal. It is also a potent inhibitor of the enzyme histone deacetylase. Depsipeptide has shown potent antitumor effects in vitro against tumor cell lines and in vivo in murine and human tumor xenograft model.

Objectives
• To calculate the confirmed response (complete and partial) probability in patients with metastatic or locally advanced, unresectable colorectal cancer who are treated with depsipeptide.
• To assess the time to treatment failure and overall survival for this group of patients.
• To assess the qualitative and quantitative toxicities associated with this regimen.

Statistical Endpoints
The primary goal of this study was to evaluate the confirmed response probability in advanced colorectal cancer patients with treated with depsipeptide. It was assumed that this therapy would be of no further interest if the true response probability was 5% or less, and of interest if the true response probability was 20% or more. The study had a two-stage design, requiring at least one response out of the first 20 to allow accrual to the second stage, with five or more of the total 40 considered evidence that this regimen was of interest in advanced colorectal cancer. Forty patients would be sufficient to estimate the probability of a particular toxicity to within ± 16%.

Results and Conclusions
Twenty-five evaluable patients were accrued to the first stage. No objective responses were observed, and the study was permanently closed. Four patients had stable disease as the best response. Twenty-five patients were assessed for toxicity. No grade 4 or greater toxicities were seen. Depsipeptide at this dose and schedule was considered to be ineffective in the treatment of patients with metastatic colorectal cancer after prior chemotherapy. Future trials might evaluate combinations of depsipeptide with chemotherapeutic or other agents.
S0356: Phase II Study of Oxaliplatin Plus Protracted Infusion 5-Fluorouracil and Radiation for Potentially Curable Esophageal Cancer (Activated 9/15/04; Closed 8/1/08)

Schema

Pre-registration Biopsy
Registration

Chemotherapy plus Radiation  Oxaliplatin 85mg/m2 d1,15,29
5-FU 180 mg/m2/d d8-43
Radiation 4500 cGY begins d8

Repeat biopsy and clinical evaluation and assessment.
Patients with stable disease or better go on.
All others removed from protocol treatment

Surgery (wks 4-10)

Chemotherapy wks 4-10 after surgery
 Oxaliplatin 85mg/m2 d1,15,29
 5-FU 180 mg/m2/d d1-36

Rationale

The standard curative approach to esophageal cancer is surgery alone or cisplatin-based chemoradiation alone. Pre-operative treatment has recently been incorporated into care of these patients as standard of care in the United States. However, the toxicity of cisplatin in these often tenuous patients frequently limits the administration of optimal therapy. A single institution phase I study revealed promising results with 5-FU/oxaliplatin in this population of patients in combination with radiation, with a pathologic CR rate of 32%. This study was pursued to confirm the pathologic CR rate and identify a neoadjuvant regiment that would be better tolerated. The overarching translational goal is to identify a molecular correlate or set of molecular correlates that suggest either efficacy or resistance to the often used fluoropyrimidine, platinum and radiation treatment regimen.

Objectives

- The primary objective was to assess the pathologic complete response probability
- Secondary objectives were to assess the frequency and severity of toxicities with this regimen
- To assess the overall survival
- To assess progression-free survival in this group of patients
- Correlative: To assess molecular correlates preliminarily, including mRNA levels of TS, ERCC-1 XPD, and XPA and response and survival in patients with adenocarcinoma of the esophagus treated with 5-FU/oxaliplatin and external beam radiation and to explore the time-dependent (pre-treatment and post-treatment) expression of mRNA in these same markers and to explore the association between specific genetic polymorphisms of TS and ERCC-1 and esophageal tumor response and overall survival for patients receiving this therapy.

Statistical Endpoints

It was assumed that this therapy would be of no further interest if the true pathologic CR probability is <25% and of interest if the true pathologic CR probability >40%. A two-stage design was to be used. 29 or more responses out of a total 85 eligible patients would demonstrate that this regimen is of interest. The design had a power of 89% when the true pathologic CR probability is 40% and a significance level of 0.04.

Results and Conclusions

With 56 patients entered, the trial was temporarily closed and then reopened when it was shown that the pCR rate > 25% for those entered onto the trial. These were all reviewed by SWOG Central Pathology. The toxicity was tolerable, though there was one postoperative death. Postoperative therapy, as mandated by protocol, was not administered to approximately 40% of eligible patients. The trial has recently met accrual goals and was closed August 1, 2008 with 98 patients accrued (6 are ineligible and 12 pending eligibility review). Final efficacy and correlative results await mature data; however, the encouraging preliminary data from this trial has led to CTEP approval for a combined phase II effort between SWOG and ECOG. Findings have been submitted for possible presentation at the 2009
American Society of Clinical Oncology meeting.

**S0413: Phase II Study of GW572016 (NSC-727989) as First Line Therapy in Patients with Advanced or Metastatic Gastric Cancer** (Activated: 12/15/05; Closed: 5/15/06)

**Schema**
GW572016 was administered to chemo-naive metastatic gastric cancer patients at a dose of 1500 mg orally daily. A cycle was defined as 28 days of therapy, and patients were staged after 2 cycles of treatment.

**Rationale**
Many chemotherapeutic drugs have single-agent activity in advanced disease, including fluoropyrimidines, platins, CPT-11, taxanes and adriamycin. Although response rates with combination cytotoxics range from 30 to 50%, there can be significant toxicity associated with these regimens, and median survival remains between 6 and 9 months. A potential therapeutic target was the epidermal growth factor receptor, as expression of EGF and its receptor has been found to correlate with prognosis in patients with gastric cancer and a significant number of gastric cancer cell lines express EGFR, which grow in response to EGF/TGF-. Additionally, over-expression of HER2 is related to poor prognosis in some solid tumors, though studies of its effect on gastric cancer revealed conflicting results. In the laboratory, the combination of anti-EGFR and anti-ErB2 mAbs results in additive anti-proliferative effects, suggesting a potential benefit of this combined therapy in the treatment of cancers stimulated by EGFR and HER2 signals. Finally, GW572016 was a dual tyrosine kinase inhibitor of both EGFR and HER2/erB2. Treatment with GW572016 in tumor xenografts that over-expressed both EGFR and HER2 resulted in reduced levels of phosphorylated tyrosine, which correlated with inhibition of tumor growth.

**Objectives**
- The primary objective of this study was to assess the confirmed response (complete and partial) probability in patients with advanced/metastatic gastric cancer treated with GW572016.
- The secondary endpoints include time to treatment failure
- Overall survival
- Qualitative and quantitative toxicities associated with this regimen
- To perform an assessment, in a preliminary manner, of the relationship of protein expression and gene expression of EGFR, HER2 and markers of angiogenesis and downstream regulatory markers with clinical outcome in patients treated with GW572016.

**Statistical Endpoints**
A two-stage design was used to detect a difference in the null hypothesis of 5% response probability and the alternative 20% response probability. If at least one response occurred after the first 20 pts, another 20 were to be accrued.

**Results and Conclusions**
The study met its first stage goal, and continued until full accrual. The study accrued 47 pts from February 2005 until May 2006. Two patients lacked required tissue/blood submission but are included in this clinical analysis. One patient did not receive treatment and is not analyzable. Pt characteristics: male/female30/16 (65%/35%); median age 68.7 years (range 38.9 – 90). Significant toxicities: 1 grade 4 cardiac ischemia/infarction, 2 grade 4 fatigue, 1 grade 4 vomiting.
There was one treatment related death due to CNS ischemia. Three pts (7%) had a confirmed PR and 2 (5%) unconfirmed PR, and 9 (20%) had stable disease. The observed number of responses failed to meet the criteria set in the study design. Median TTF was 2 months, and OS was 5 months. Molecular correlative data was available on 42 pts.

Tumor tissues were successfully collected from 35 of 43 patients and blood samples from 42 of 43 patients. There was a significant association of the median her2 and Il-8 gene expression levels with median survival in this patient population. Germ-line polymorphisms of Il-8 associated with Il-8 expression were also associated with overall survival.

GW572016 was felt to be a well-tolerated agent with modest single-agent activity in patients with advanced/metastatic gastric cancer. This trial was the first to demonstrate molecular markers associated with survival in patients treated with lapatinib.
S0414: Cetuximab plus Cisplatin, Irinotecan and Thoracic Radiotherapy for Locally Advanced, Non-Metastatic, Clinically Unresectable Esophageal Cancer: A Phase II Trial with Molecular Correlates (Activated 5/1/05; Closed 9/1/07)

**Schema**

Weeks 1-6: Pre-treatment
2 cycles of chemotherapy with cetuximab, cisplatin and irinotecan

Weeks 7-12: Pre-treatment
2 additional cycles of chemotherapy with cetuximab, cisplatin and irinotecan
Concurrent radiation

Week 16: re-evaluation

**Rationale**

Combination therapy with chemotherapy and radiation, +/- resection, is recommended as definitive treatment of loco-regionally advanced, non-metastatic esophageal cancer. The irinotecan/cisplatin/radiation regimen was evaluated in a phase I study and was associated with a pCR rate of 32%. The over-expression of EGFR has been shown in over 90% of esophageal cancer, and the EGFR inhibitor cetuximab is a potent radiosensitizer.

**Objectives**

- To assess 2 year overall survival of combination cetuximab, cisplatin, irinotecan with radiation as definitive treatment of patients with locally advanced disease.
- To assess the toxicity of this regimen
- To assess the objective response probability in patients with measurable disease
- To assess in a preliminary manner, markers of response, time to progression, overall survival and toxicity including: Associations between markers and outcome will be evaluated, DNA repair (ERCC-1, XRCC-1), drug metabolism (UGT1A1) and the EGFR pathway (EGFR, IL-8, VEGF).

**Statistical Endpoints**

Patients with adenocarcinoma of the esophagus represented the stratum assessed for the primary endpoint. Patients with squamous cell carcinoma were included in overall descriptive statistics of the study. The therapy was to be considered of no further interest if the true overall survival at 2 years is 35% or less, but considerable interest if the true overall survival at 2 years were 50% or more. 75 patients were to be accrued.

**Results and Conclusions**

Although activated in May 2005, this trial accrued slowly. Several discussions within the SWOG GI Committee regarding the viability of this trial were undertaken. Initially it was decided to continue the trial because it was likely to accrue a minority, underserved population that has historically shown a very poor prognosis for esophageal cancer. Unfortunately, accrual did not improve significantly and the trial closed in 9/2007. The reasons for failure may have been related to the regimen chosen. Generally these are patients may have borderline performance status and although an established regimen, clinicians may be biased to the tolerability of cisplatin/irinotecan/cetuximab and radiation.
**S0415: Phase II Trial of Cetuximab as Second Line Therapy in Metastatic Esophageal Cancer** (Activated: 10/15/04; Closed 1/1/07)

**Schema**

<table>
<thead>
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<th>Route</th>
<th>Day</th>
<th>Schedule</th>
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</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>400 mg/m²</td>
<td>IV over 2 hrs</td>
<td>1</td>
<td>One time only</td>
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<td></td>
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</tr>
<tr>
<td>Cetuximab</td>
<td>250 mg/m²</td>
<td>IV over 1 hr</td>
<td>8, 15, 22, etc.</td>
<td>q 7 days</td>
</tr>
</tbody>
</table>

Treatment continued until progression or unacceptable toxicity.

**Rationale**
The prognosis for patients with metastatic esophageal cancer is poor, with a median survival of 6-8 months. Although there were several trials demonstrating activity of chemotherapy in first line setting, little data existed on the benefit of second-line therapy, with studies suggesting median survivals of 5-5.6 months. Over-expression of the EGFR has been demonstrated in 92% of esophageal cancers. Blockade of this receptor with monoclonal antibodies such as cetuximab leads to cell cycle arrest in G1 that is accompanied by a decrease in cyclin dependent kinase activity and an increase in the expression of CDK inhibitor p27KIP1 and apoptosis. In a phase I trial of anti-EGFR therapy in patients with advanced cancer, it was demonstrated that one out of three esophageal cancer patients had stable disease for seven months. Therefore given the poor prognosis of patients with advanced esophageal cancer, coupled with the preclinical and clinical rationale for EGFR antagonists, this phase II trial was performed.

**Objectives**

- To assess the six-month overall survival
- To assess ORR
- To assess TTP
- To assess TTF
- To assess toxicity
- To assess, in a preliminary manner, the relationship of gene expression and germ line polymorphism of enzymes and genes involved in the EGFR pathway, DNA repair and angiogenesis to efficacy and toxicity parameters.

**Statistical Endpoints**
The accrual goal was 55 eligible patients, with a two-stage design. If after the first 30 pts, at least nine survived past 6 months, an additional 25 were to be accrued. This therapy would be of interest if 6-month OS rate is > 42%. The trial had 90% power to detect a true six month overall survival probability of 50%, at a significance level of 0.04.

**Results and Conclusions**
Sixty-three patients were registered, 8 were not eligible. 55 eligible pts (male=49, female=6), median age 61.2 years (range 30.7-88.5) were enrolled. Out of 55 eligible and evaluable pts, there was one partial response and 2 unconfirmed partial responses. 20 survived > 6 months for a 6-month overall survival rate of 36% (95% CI: 24%, 50%). The median overall survival was 4 months (95% CI: 3.2, 5.9), and the median progression-free survival was 1.8 months (95% CI: 1.7, 1.9). Two pts experienced Grade 4 fatigue, and there was one treatment-related death due to pneumonitis. Four pts had Grade 3 rash, and three of them survived > 6 months. There was adequate tissue was available for analysis in 42/55 patients. Evaluation of germ-line polymorphisms of EGFR, EGF, II-8, COX-2, VEGF, cyclin D, NRP and k-ras mutational status did not demonstrate any association with clinical outcome. Only one patient out of 42 patients had a kras mutation.

This clinical trial was the first attempt for a cooperative group to define a role for a targeted agent against esophageal cancer. This trial did not meet the primary objective of 23 pts surviving beyond 6 months, and thus could not lead to the conclusion cetuximab alone could be recommended in the second-line treatment of metastatic esophageal cancer. However, given that this agent was associated with a 36% 6-month survival rate, and that it was well tolerated, trials combining cetuximab with cytotoxic chemotherapy in metastatic esophageal cancer are reasonable and are being pursued in the Intergroup.
S0425: Neoadjuvant Chemoradiation Therapy with Oxaliplatin and Capecitabine for Patients with Surgically Resectable Gastric Cancer: A Pilot Phase II with Molecular Correlates.  (Activated 5/1/06; Closed 1/15/08)

Schema
None available

Rationale
The benefit of post-operative chemoradiation following resection of gastric cancer was demonstrated in SWOG 9008 (INT-0116). Based on this study, post-operative chemoradiation became the standard of care in the United States. Unfortunately, in this study, only 64% of patients completed treatment as planned. Neoadjuvant chemoradiation offered potential benefits, including down-staging, assuring treatment in patients who may have better performance status pre-op, continuing treatment in those that benefited, and allowing patients with rapidly progressive disease to be identified. Thus this study was performed to assess a potentially better tolerated regimen with oxaliplatin and capecitabine, utilized in the pre-operative setting with radiation, to assess the impact on overall outcome in patients with potentially resectable gastric cancer.

Objectives
· To determine the pathologic complete response rates of primary gastric adenocarcinoma treated with capox followed by cape/XRT pre-operatively.
· To assess the toxicities associated with this regimen.
· To explore in a preliminary manner several molecular markers including comparative genomic hybridization; genes associated with platinum, 5-FU and angiogenic factors; haplotypes of several candidate genes.

Statistical Endpoints
The primary endpoint was to evaluate the pathologic complete response rate following neoadjuvant therapy with oxaliplatin and capecitabine followed by radiation and concurrent capecitabine in patients with adenocarcinoma of the stomach. It was assumed that this regimen would be of further interest if the pCR were 25% or greater and of no further interest if it were 12% or less. The study had a one-stage design, in which 75 patients were proposed to be accrued. 15 or more responses of this 75 would be considered evidence that this regimen is of interest. The design has a power of 92%, when the true pCR rate is 25%, significance level of 0.06. Although the study had a one stage design, an interim assessment of response was to be done after 30 patients were accrued. If 2 or fewer pCR’s were noted, the study was to be closed.

Results and Conclusions
After 18 months the trial had accrued only 7 patients and therefore was closed. The trial was analyzed with respect to reasons for failure. Proposed reasons included the requirement for laparoscopic evaluation, toxicity fears from use of preoperative radiation therapy as opposed to chemotherapy alone, and reliance on surgeons to send their patients to medical oncology/radiation oncology prior to surgery, which is not the current approach to therapy in the United States.

SWOG-0514: A Phase II Study of Sorafenib as a Single Agent in patients with Unresectable or Metastatic Gallbladder Cancer or Cholangiocarcinoma (Activated: 10/1/05; Closed to patient entry: 01/1/07)

Schema
Single arm: Sorafenib 400 mg PO BID continuously; One cycle=28 days

Rationale
Cytotoxic chemotherapy combinations have shown a modest benefit in patients with advanced gallbladder adenocarcinoma and cholangiocarcinoma. Response rates range between 10 and 30% as reported in multiple small phase II studies. The same studies report overall survival results that range
between 6 and 12 months. At the time of the design of this study, there were emerging data regarding the molecular carcinogenesis of biliary cancers. For example, BRAF mutations were noted in 15 out of 69 (22%) patients with cholangiocarcinoma. VEGF was found to be expressed in 19 out of 19 tumor specimens from patients with cholangiocarcinoma. Given the activity of Sorafenib as an oral inhibitor of RAF kinases and vascular endothelial growth factor receptor 2 (VEGFR-2), SWOG designed a phase II study of sorafenib as a single agent in patients with unresectable or metastatic gallbladder carcinoma and cholangiocarcinoma.

**Objectives**

- To assess the objective response probability for sorafenib in patients with unresectable or metastatic gallbladder and cholangiocarcinoma
- To assess the overall survival, time to treatment failure and progression-free survival in these patients
- To assess quantitative and qualitative toxicities of this regimen
- To evaluate in a preliminary fashion relevant prognostic and predictive molecular markers of clinical outcome

**Statistical Endpoints**

A two-stage design was used to evaluate the response in the entire population. If, after the first 25 patients, at least one confirmed response were to be observed, the study was to accrue 25 more patients. Six or more responses out of the total of 50 would be considered evidence that this regimen is of interest in unresectable/metastatic gallbladder carcinoma and cholangiocarcinoma.

**Results and Conclusions**

The study was permanently closed after the first stage of accrual due to failure to meet the response end point. Thirty six patients were accrued between October 2005 and July 2006. Five patients were ineligible for response and toxicity assessment. 2 patients (6%) had an unconfirmed response and 10 (32%) had stable disease. The median overall survival (OS) was 9 months (95% CI: 4-9 months) and the progression free survival (PFS) was 3 months (95%: 2-4 months).

Although the study failed to meet its primary response endpoint, the OS and PFS were comparable to results reported with cytotoxic chemotherapy combinations, such as gemcitabine and capecitabine. Correlative studies that include the evaluation of B-raf mutational status, VEGF serum level and VEGFR2 gene expression were planned and received TRI funding. However, this funding was subsequently discontinued due to budget limitations; alternate sources of funding are being sought to complete these exploratory studies.
Current Studies

S0502: Phase III Trial of Imatinib Mesylate, plus or minus Bevacizumab, in Patients with Incurable Gastrointestinal Stromal Tumors (Activated 4/15/08; Currently accruing)

Schema:

```
R A N D O M I Z A T I O N

Arm 1: Imatinib, po continuously
       Bevacizumab IV q3 weeks

Arm 2: Imatinib, po continuously
```

Rationale

Angiogenesis is an important process in GIST, and it is correlated with poor prognosis. Bevacizumab is a potent inhibitor of the VEGFR, and it can be safely administered with imatinib mesylate, the therapy of choice in untreated incurable GIST.

Objectives

- To determine whether treatment with imatinib plus bevacizumab leads to improved PFS versus treatment with imatinib alone in first-line treatment of incurable GIST.
- To compare ORR and overall survival
- To compare the frequency and severity of toxicities associated with imatinib plus bevacizumab versus imatinib alone.
- To compare response assessment per RECIST to a modified MD Anderson criteria system.
- To explore the association between soluble VEGF, VEGF-D, VEGFR-1, VEGFR-2, angiopoietin-2 (Ang-2), PDGFR-AA and PDGFR-BB levels, PET imaging and immunohistochemistry for p16, VEGF and VEGFR, with kinase mutation status and clinical outcomes.
- To explore imatinib pharmacokinetics with single nucleotide polymorphisms involving the ABCG2 and CYP3A4 genes, as well as other genes that are reported to influence the absorption, distribution, metabolism and elimination of imatinib.

Statistical Endpoints

The primary objective of the study is to determine if the addition of bevacizumab to imatinib improves the progression-free survival of patients with unresectable or metastatic GIST. Assuming exponential progression-free survival and an 18 month progression-free survival median on the imatinib arm, then four years of accrual (total of 572 eligible patients) and 2 additional years of follow-up will be required for a one sided .025 level stratified log rank test to have power .85 for detecting a 33% improvement due to the addition of bevacizumab. Assuming exponential survival and a 2 year overall survival of 70% then 572 patients will also have 74% power to detect a 33% increase in median overall survival at the one-
sided 0.05 level. Assuming approximately 80% of patients have measurable disease, a sample size of 230 patients per arm is sufficient to estimate response probabilities to within at worst ± 6%.

**Results and Conclusions**
This is an ongoing study, and no results are currently available.

**S0518**: Phase III Prospective Randomized Comparison of Depot Octreotide Plus Interferon Alpha Versus Depot Octreotide Plus Bevacizumab (NSC #704865) in Advanced, Poor Prognosis Carcinoid Patients (Activated 12/1/07; Currently accruing)

**Schema**

![Schema diagram](image)

**Rationale**
Effective systemic therapy for advanced carcinoid is lacking. The combination of bevacizumab (BEV) and pegylated (PEG) interferon alfa-2b was evaluated among patients with metastatic or unresectable carcinoid tumors in a pilot clinical trial by SWOG investigators. PFS rates after 18 weeks of monotherapy were 95% in bevacizumab versus 68% on the PEG interferon arm. There was also a significant decrease in tumor blood flow at day 2 and week 18 only among bevacizumab-treated patients. Yao J Clin Oncol 2008.

**Objectives**
- Primary objective: To compare central review-based PFS between the two arms
- Overall survival
- TTF
• PFS
• ORR
• Toxicity profile.
• Correlative: Prognostic and predictive values of VEGF expression; assessment and comparison of responses among patients with elevated 5HIAA, chromogranin A or neuron-specific enolase levels at baseline between treatment arms; prognostic and predictive value of In-111 pentetreotide somatostatin-receptor scintigraphy (SRS) and CT vs. CT

Statistical Endpoints
The primary objective is to compare PFS. It is assumed that the median PFS in the octreotide/interferon group will be 6 months, and an improvement of 50% (a hazard ratio of 1.5, corresponding to an improvement to a median of 9 months) would be of clinical interest. 283 patients will be sufficient with 90% power, based on a two sided .05 level test. Overall survival, time to treatment failure, traditionally reported progression-free survival, objective response and toxicity will be evaluated as secondary endpoints.

Results and Conclusions
This trial is ongoing, and no results are currently available.

C80405*: A Phase III Trial of Irinotecan/5-FU/Leucovorin or Oxaliplatin/5-FU/Leucovorin with Bevacizumab, or Cetuximab (C225), or with the Combination of Bevacizumab and Cetuximab for Patients with Untreated Metastatic Adenocarcinoma of the Colon or Rectum. (Activated: 10/01/05; Temporarily Closed: 06/06/08)

*Co-led by CALGB and SWOG; SWOG conducting the correlative work.

Schema

1 Cycle = 8 Weeks

**ARM A**
Bevacizumab 5 mg/kg IV every 2 weeks followed by FOLFOX or FOLFIRI* every 2 weeks.

**ARM B**
Cetuximab 400 mg/m² IV on Day 1 of Cycle 1 only, then 250 mg/m² IV weekly followed by FOLFOX or FOLFIRI* every 2 weeks.

**ARM C**
Cetuximab 400 mg/m² IV on Day 1 of Cycle 1 only, then 250 mg/m² IV weekly followed by Bevacizumab 5 mg/kg IV every 2 weeks, followed by FOLFOX or FOLFIRI* every 2 weeks.

* The decision to use either FOLFOX or FOLFIRI is at the patient/treating physician’s discretion, but must be declared prior to registration and must not be changed during the course of the patient’s treatment.
Rationale
FOLFOX or FOLFIRI, with bevacizumab represent standard of care therapy for untreated colorectal cancer patients. Both chemotherapies can be effectively and safely combined with cetuximab. Finally, the combination of cetuximab and bevacizumab is highly effective and relatively non-toxic in advanced disease patients. This study will explore the possibility that the addition of cetuximab to either of the chemotherapy combinations or to the chemotherapy and bevacizumab combinations will lead to a superior outcome compared to chemotherapy with bevacizumab. Correlative studies will attempt to identify predictors of response to these therapies and will also look to confirm the reported 70% incidence of EGFR positivity in patients with advanced colorectal cancer.

Objectives

- To determine if the addition of cetuximab to FOLFIRI or FOLFOX chemotherapy with or without bevacizumab prolongs survival compared chemotherapy with bevacizumab.
- To determine the rate of down-staging to resectability.
- To compare the effect of different combinations of chemotherapy and biologic agents on resource utilization, cost, and utilities, and if applicable, to make estimates of marginal cost-utility.
- To prospectively assess the influence of diet, obesity, physical activity, and other lifestyle habits on treatment-related toxicity, progression-free survival and overall survival in patients with stage IV colorectal cancer.
- To prospectively assess whether tumor expression of tissue-based markers can independently predict for efficacy.
- To prospectively assess whether markers of epidermal growth factor receptor (EGFR) activity, including tumor IHC analysis of COX-2, AKT-p-Ser473, and p44/42 MAP kinase and EGFR expression, are independent predictors of a variety of efficacy parameters.
- To create tissue microarrays (TMAs) containing both tumor and non-tumor samples from each patient treated on this protocol.

Statistical Endpoints
Sample size is based on the primary endpoint, OS. A median OS of 22 months is assumed in the chemotherapy + bevacizumab treatment group. With a total of 2,289 patients enrolled over 30.5 months and 24 months of follow-up 90% power is achieved to detect a hazard ratio of 1.25. One thousand four hundred seventy-eight (1,478) events are expected in the three treatment arms, 1,006 for each comparison, at the time of final analysis.

Results and Conclusions
To date, this trial has accrued 1419 patients (422 from SWOG). This trial was temporarily closed on June 6, 2008 due to the emerging data on K-ras mutation status and the efficacy of anti-EGFR targeted therapy. The trial re-opened to include only patients with tumors expressing wild-type RAS. No results are yet available.

SWOG 0600: Phase III Trial of Irinotecan-Based Chemotherapy plus Cetuximab (NSC-714692) versus Irinotecan-Based Chemotherapy plus Bevacizumab (NSC-704865) as Second-line Therapy for Patients with Metastatic Colorectal Cancer who have Progressed on Bevacizumab with either FOLFOX, OPTIMOX or XELOX. Co-led SWOG and NCCTG
Schema

Metastatic colorectal cancer with disease progression on first-line chemotherapy with Bevacizumab and either FOLFOX, OPTIMOX, or XELOX

Rationale
First-line therapy with bevacizumab improves survival in metastatic colorectal cancer, and is now standard practice. ECOG 3200 also showed that second-line therapy with bevacizumab is also acceptable. The EPIC trial demonstrated that the addition of cetuximab to irinotecan improves PFS in second-line therapy. However, the optimal choice of biologic for second-line therapy is unknown. SWOG 0600 was amended, as recently presented studies failed to demonstrate improvements in outcome with combination biologic therapy. Similarly, the emerging Kras data mandated a change to the study as well, which now requires patients with Kras WT tumors. Finally, the dose of bevacizumab has been clarified at 5mg/kg.

Objectives
In patients with KRAS wild type metastatic colorectal cancer who progressed on first line therapy with bevacizumab plus either FOLFOX, OPTIMOX or XELOX, to compare progression-free survival among those treated with irinotecan-based chemotherapy plus cetuximab to those treated with irinotecan-based chemotherapy plus bevacizumab.

- Overall Survival
- Response Rate
Statistical Endpoints

This trial has been extensively amended based on emerging data on tumor RAS status. The current proposed primary objective is to compare progression-free survival (PFS) in patients with KRAS wild type advanced/metastatic colorectal cancer treated with FOLFIRI or irinotecan plus either cetuximab or bevacizumab. The bevacizumab arm will be considered superior if the median progression-free survival increases with a hazard ratio of 1.3, corresponding to a change from 5 months to 6.5 months.

With a commitment of participation by NCCTG, NCIC, CALGB and ECOG, and increasing interest in the role KRAS plays in the identification of patient response to cetuximab, we anticipate a combined accrual of at least 35-40 patients a month. With 3 years of accrual and an additional 2 years of follow-up, 620 patients will be sufficient to detect a 1.3 hazard ratio with 90% power, based on a two-sided 0.05 stratified test.

We will also perform secondary analysis of overall survival. With 620 patients, we will have 86% power to detect a 1.3 hazard ratio (corresponding to 12 month median survival in the cetuximab arm, and 15.6 in the bevacizumab arm).

Results and Conclusions

To date, this trial has accrued 51/1260 patients. This trial was temporarily closed on June 6, 2008 due to the emerging data on K-ras mutation status and the efficacy of anti-EGFR targeted therapy. No results are yet available.

SWOG S0727:  A Phase I and Randomized Phase II Trial of Gemcitabine + Erlotinib (NSC-71817 + IMC-A12 (NSC-742460) vs. Gemcitabine + Erlotinib as First Line Treatment in Patients with Metastatic Pancreatic Cancer (Activated 03/01/2008).

Schema
None available

Rationale

The insulin-like growth factor-1 receptor (IGF-1R) and its ligands insulin like growth factors I and II have been implicated by large numbers of studies in the development, maintenance, and progression of cancer. It also plays a role in the resistance mechanisms to several anticancer agents. Inhibition of IGF-1R signaling has been linked to the inactivation of the PI3K/AKT pathway and enhances apoptosis in radiation- or chemotherapy-treated tumor models including gemcitabine-treated pancreatic cancer xenografts. It also can prevent, delay, or reverse resistance to EGFR small-molecule inhibitors. The antibody IMC-A12 binds to IGF-1R and blocks ligand binding to the receptor and also causes internalization and degradation of the receptor. IMC-A12 has shown tumor growth inhibition in a wide range of in vitro and in vivo models. Enhanced anti-tumor activity is seen when it is combined with chemotherapy or inhibitors of the EGFR pathway.

Objectives

Part I:

- To assess the appropriate dose of IMC-A12 to use in combination with gemcitabine and erlotinib.

Part II:

- To assess progression-free survival in patients with metastatic pancreatic cancer treated with IMC-A12 plus gemcitabine and erlotinib compared to those treated with gemcitabine
and erlotinib alone.

- To assess overall survival in each of the two treatment arms in this group of patients.
- To assess the total response probability (confirmed and unconfirmed. Complete and partial responses) in each of the two treatment arms in the subset of this group of patients with measurable disease.
- To assess the qualitative and quantitative toxicities in each of the two treatment arms in this group of patients.
- To assess potential relationships between gene expression levels, germ-line polymorphisms and Ras and PI3K mutations with PFS and OS.

**Statistical Endpoints**

Phase I study: Initially, patients will be treated at an IMC-A12 dose of 6 mg/kg. If this dose is not tolerated, then 4 mg/kg and (if necessary) 3mg/kg will be explored. Ten patients will be evaluated at the recommended dose prior to opening the Phase II portion of the trial.

Phase II study: Based on previous studies, expected median PFS is approximately 2 months. Based on a type 1 error of 10% and 90% power, and assuming approximately 1.5 years of accrual and 1 year of follow-up, 106 patients are required to detect an improvement from 2 months to 3.3 months (hazard ratio 1.65). This sample size would also have approximately 82% power to detect a 1.6 hazard ratio for OS (corresponding to an improvement from median of 6 months to median of 9.6 months) Any toxicity with an occurrence rate of at least 5% is highly likely (0.94) to be seen at least once.

Correlative studies will be exploratory in nature; for preliminary explorations measures such as gene expression may be categorized but defining high/low values as the median. These explorations will initially be done separately within treatment arms; the trial will also explore the potential predictive value of the markers to determine improvement due to IMC-A12 by assessing interactions between treatment and marker using a Cox regression model. However, since the power to detect main effects and interactions is quite small, these analyses will be used to identify potential hypotheses to be validated in future studies.

**Results and Conclusions**

As of this submission, this trial is nearing completion of the phase I portion. It is expected to begin phase II accrual prior to the site visit. No results are as of yet available.

**Future Studies**

**S0713: A Phase II Study of Oxaliplatin and Capecitabine in Combination with Cetuximab and Radiation in Pre-Operative Therapy of Rectal Cancer**

**Schema**

Pre-registration biopsy and specimen submission for k-ras mutation analysis

Registration
Chemotherapy Cycle 1

Chemotherapy Cycle 2 plus radiation

Restaging and preoperative evaluation

Tumor resection

**Rationale**

The vast majority of rectal cancer patients are treated with chemotherapy and radiation in conjunction with surgery, either in the adjuvant setting, or for control of local disease in the disseminated disease setting. Increasingly, neoadjuvant chemoradiation is being employed for the former. The standard chemotherapy (protracted infusion 5-fluorouracil (PIFU) with irradiation offers a complete response rate of 15-25%. Cetuximab improves efficacy of 5FU-platinum regimens in the setting of metastatic disease, and it is a potent radiosensitizer.

**Objectives**

- To assess the pathologic complete response rate for the combination of oxaliplatin, capecitabine and cetuximab alone and concomitantly with external beam radiation (EBRT) pre-operatively for patients with adenocarcinoma of the rectum, Stages II and III with wild-type K-ras.
- To estimate the 3-year disease-free survival probability
- To assess the frequency and severity of toxicities associated with the combination of oxaliplatin, capecitabine and cetuximab alone and concomitantly with external beam radiation.
- To explore in a preliminary fashion the association between expression levels of genes involved in the DNA repair, EGFR, angiogenesis and 5-FU pathway (such as TS, ERCC-1, TP, DPD, GST-P1, XPD, EGFR, VEGF, IL-8 and Cox-2) and pathologic complete response.
- To explore in a preliminary fashion the intratumoral gene expression levels of genes involved in the DNA repair, EGFR, angiogenesis and 5-FU metabolic pathway (such as TS, ERCC-1, TP, DPD, GST-P1, XPD, EGFR, VEGF, IL-8 and Cox-2) following completion of all treatment in this protocol.
- To obtain preliminary data on genomic polymorphisms of genes involved in the DNA repair, EGFR, angiogenesis and 5-FU metabolic pathway (such as TS, ERCC-1, EGFR, GST-P1, XPD, VEGF, TGF- and COX-2) for correlation with clinical outcome and toxicity.

**Statistical Endpoints**

It is assumed that the proposed regimen will be of further interest if the pCR probability is 30% or greater and of no further interest if it is 15% or less. Eighty patients with stage II or III adenocarcinoma of the rectum and wild-type k-ras will be accrued, in two stages. Eighteen or more responses out of 80 will be considered evidence that this regimen is of interest. This design with 80 eligible patients has a power of 94%, when the true pCR probability is 30%, and a significance level of 0.05.

**Results and Conclusions**

This study should be activated in early 2009.
S0809: A Phase II Trial of Adjuvant Capecitabine/Gemcitabine Chemotherapy Followed by Concurrent Capecitabine and Radiotherapy in Extrahepatic Cholangiocarcinoma (EHCC)

**Schema**

R0 or R1 resection → 4 cycles (12 weeks) of gemcitabine and capecitabine chemotherapy → capecitabine concurrently with radiation therapy for 5-6 weeks

**Rationale**

The overall prognosis for patients with EHCC is poor with 5-year survival rates of 5-19%. While complete resection is the most effective and the only potentially curative treatment, the local and distant/systemic relapse rates are high. The role of chemotherapy and/or radiotherapy as adjuvant treatment in resected EHCC is not clear. Existing literature regarding post-operative adjuvant treatment consists of mostly single-institution retrospective reviews plagued by heterogeneity of selection criteria and treatment. Some of these reviews suggest a benefit to adjuvant radiotherapy or chemoradiotherapy. This phase II study is designed to attempt to address the lack of prospective data on adjuvant therapy in patients with EHCC, using a modern drug combination of capecitabine and gemcitabine.

**Objectives**

- To estimate the stratum-specific (R0 and R1) and overall 2-year survival probabilities of EHCC patients treated with adjuvant capecitabine/gemcitabine followed by capecitabine and radiotherapy
- To estimate the 2-year stratum-specific and overall disease-free survival and local disease-free survival attained with this regimen
- To assess the frequency and severity of toxicity associated with this regimen

**Statistical Endpoints**

According to SEER, the 2-year relative survival rate for patients with localized gallbladder cancer is 56%, while it is only 25% for those with regional disease. Approximately 20% of patients are diagnosed with local disease and 40% with regional disease. Pooled results from multiple single-institution reports suggest a 2-year survival of 55% and 38% for R0 and R1 resections respectively, and a 40% R0 resection rate. In order to assure adequate precision of the 2-year stratum-specific survival probabilities, 80 patients will be accrued, with a minimum of 35 patients within each stratum. With 35 patients, 2-year survival probabilities within the range suggested can be estimated to within ± 17% based on an approximate 95% confidence interval. With 45 patients, the precision is improved to within ± 15%. The pooled 2-year survival probability using all 80 patients will be estimated to within ± 12%.

**Results and Conclusions**

This study has been approved by CTEP and should activate shortly.

SWOG09-TBD A Phase II Study of Sorafenib in Combination with Erlotinib in Patients with Unresectable or Metastatic Gallbladder Carcinoma and Cholangiocarcinoma

**Schema**

TBD

**Rationale**

Both sorafenib and erlotinib have shown modest activity as single agents in patients with metastatic...
biliary cancers. SWOG-0514 was a phase II study that evaluated the role of single agent sorafenib in patients with unresectable or metastatic gallbladder carcinoma and cholangiocarcinoma, and it revealed a median PFS of 3 months and median OS of 9 months, comparable to results seen with modern cytotoxic chemotherapy combinations. EGFR, VEGF, and HER2 are over-expressed in 27.4, 53.8, and 0.9% of intrahepatic cholangiocarcinoma (IHCC), and 19.2, 59.2, and 8.5% of extrahepatic cholangiocarcinoma (EHCC), respectively. Clinicopathologically, EGFR over-expression is associated with lymph node metastasis and advanced tumor stage and VEGF over-expression with intrahepatic metastasis in IHCC. These results suggest that EGFR expression is associated with tumor progression and VEGF expression may be involved in hematogenous metastasis in cholangiocarcinoma. In biliary cancers, targeting both pathways with the combination of bevacizumab and erlotinib has shown a response rate of 17% and time to progression of 7.5 months in an-going phase II study.

**Objectives**

- To assess the stratum-specific (IHCC and gallbladder carcinoma versus EHCC) and entire population PFS with the combination of sorafenib and erlotinib
- To assess the stratum-specific (IHCC and gallbladder carcinoma versus EHCC) and entire population overall survival in
- To assess the stratum-specific and entire population ORR
- To assess the frequency and severity of toxicity associated with this regimen

**Statistical Endpoints**

Because it is assumed that patients with EHCC have a better prognosis versus those with gallbladder or IHCC, patients will be stratified by disease type (EHCC vs. GB or IHCC). In the EHCC subgroup, it is assumed that this regimen would not be of further interest if the true median PFS were 4 months or less, while it would be of considerable interest if the true median PFS were 7 months or more. With forty patients accrued there would be 95% power to detect this difference at a significance level of .05. An observed median PFS of 5 months or more will be considered evidence that this regimen warrants further study. For patients with gallbladder or IHCC, it is assumed that this regimen would not be of further interest if the true median PFS were three months or less, while it would be of considerable interest if the true median PFS were five months or more. We will have 94% power (probability of correctly declaring an agent with a median progression-free survival of five months or more to warrant further study) to detect this difference with a significance level of .05. An observed median PFS of 4 months or more will be considered evidence that this regimen warrants further study.

**Results**

This study is being submitted to CTEP as an unsolicited LOI.

**S0205A: Predictive and Prognostic Value of Tumor K-Ras Mutation Status, Amphiregulin and Epieregulin and gene expression levels and germ-line polymorphisms involved in the EGFR and gemcitabine pathway in Advanced Pancreas Cancer: A Study of Tissues from SWOG Protocol 0205**

**Schema**

None available
Objectives

- To determine whether **EGFR expression** measured by EGFR gene copy number, mRNA expression levels and polysomy are associated with ORR, TTP, survival and toxicity.
- To determine whether **gene expression levels (RNA) in tumor tissue** in the EGFR pathway (e.g., the epithelial growth factor receptor (EGF-R, IL-8, IL-8 CXR2, VEGF, EGF, Epiregulin, Amphiregulin, IGFR) and/or mutational status of K-ras are associated with survival, PFS, ORR and toxicity.
- To determine whether **germ-line polymorphisms (DNA)** of genes involved in the EGFR pathway (e.g., the epithelial growth factor receptor (EGF-R, IL-8 and its receptors, VEGF, EGF) are associated with toxicity and clinical outcome.
- To determine whether ADCC determined by **germ-line polymorphisms (DNA)** in the FC Gamma receptor 2a, 3a and 2b are associated with toxicity and clinical outcome.

Rationale

Biomarkers to determine sensitivity or resistance to anti-EGFR therapy will help patient selection. Although the clinical results of S0205 demonstrated no significant difference in efficacy outcomes by treatment arm, it is still possible to have a marker-treatment interaction. K-ras mutations are quite prevalent in pre-neoplastic pancreatic lesions and frank cancers (frequency 75-90%). Because of the significance of k-ras within the signalling cascade of EGFR and in carcinogenesis, evaluation of K-ras mutations as potential predictive marker of EGFR targeted therapy has been suggested. The complexity of genetic mutations in signalling pathways necessitate the study of multiple molecules downstream from EGFR.

Schema

Samples collected from participants of S0205 study will be analyzed. Laser-capture micro dissection will be used to obtain tumoral and adjacent morphologically normal pancreatic tissue and subjected to RT-PCR. RNA isolation from paraffin embedded specimens will be performed. The polymorphisms in EGFR, EGF, II-8, IL-8CXCR, FCGE2a, FCGR3a, COX-2, cyclin D are single nucleotide polymorphisms and will be assessed using Taqman assays.

Statistical Plan

Efficacy analyses will be done using the Cox Proportional Hazards Model, allowing an assessment of marker effects while adjusting for treatment assignment and the effect of other known prognostic factors such as stage and age. An assessment of potential correlations between markers and stage will be performed. In general, it is reasonable to use the entire sample, unless there is evidence of interactions between the factor and treatment. In fact, a potential interaction of outcome with k-Ras status is a primary goal of this study. Potential interactions with cetuximab will be done first, and should such interactions be detected, prognostic factors will be more appropriately assessed separately. Toxicity analyses will focus on summaries based on: 1) Maximum grade experienced by a patient; and 2) maximum grade within global categories (hematologic, gastrointestinal, etc). The primary analysis of these data will involve use of logistic regression. Secondary analyses based on techniques such as ordered logistic regression will be considered.

Results

Analysis is currently underway and no results are available.
R0848: Gemcitabine, with and without Erlotinib, Followed by a Second Randomization, with and without Chemoradiation, as Adjuvant Treatment for Pancreatic Head Cancer: A Phase III RTOG/SWOG/NCIC/EORTC Study*

*Co-led by RTOG, NCIC, EORTC, and SWOG; SWOG conducting the correlative component

Schema

<table>
<thead>
<tr>
<th>First Randomization</th>
<th>Evaluate for Recurrence</th>
<th>Second Randomization (for Non Progressing Pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine x 5 cycles</td>
<td>Evaluate for Recurrence</td>
<td>1 cycle of chemotherapy versus 1 cycle of chemotherapy then XRT/capecitabine or 5-FU.</td>
</tr>
<tr>
<td>versus Gemcitabine + Erlotinib x 5 cycles</td>
<td>→</td>
<td></td>
</tr>
</tbody>
</table>

R0/R1 Resected Pancreatic Head Adenocarcinoma

1st Randomization

Gemcitabine X 5 cycles

Gemcitabine + Erlotinib X 5 cycles

Re-Evaluate

Progressive Disease → OFF Study

2nd Randomization

Gemcitabine +/- Erlotinib X 1 cycle

Gemcitabine +/- Erlotinib X 1 cycle

5FU/XRT
Objectives

- Determine whether erlotinib and/or chemoradiation can achieve a statistically significant increase in survival for patients with resected pancreatic head cancer.
- PFS
- Assessment of wild-type and mutant K-Ras status on outcome

Rationale

Despite potentially curative resection for pancreatic adenocarcinoma, the 5-year survival in these patients is <20%. The pattern of failure demonstrates both a significant component of local regional relapse (50%-85%) and distant liver/intra-abdominal failure. CONKO 1 compared adjuvant gemcitabine to no treatment after surgery, showing significant improvements in median DFS, OS, and DFS at 5 years. RTOG 9704 evaluated the addition of gemcitabine or 5FU to 5-FU-based chemoRT, showing improved OS in patients with pancreatic head tumors with gemcitabine versus 5FU. Erlotinib in combination with gemcitabine improves survival compared with gemcitabine alone for patients with advanced pancreatic cancer.

Statistical Endpoints

650 eligible patients are required to detect an increase in MST from 19 to 24.5 months [measured from the date of second randomization (chemotherapy vs. chemotherapy followed by chemoradiation) to the date of death], translating into a hazard ratio (experimental/control) of 0.77. It is projected that 20% of the patients entering the first randomization will not go on to the second randomization due to progression, death without progression, or refusal. Adjusting for this and for an ineligibility or lack-of-data rate of up to 8%, the final targeted accrual for this study will be 942 patients.

Results and Conclusions

This trial has not yet been activated. SWOG is responsible for conducting the correlative analyses.

S0915: A Phase II Trial of Cetuximab and Dasatinib as Second-Line Therapy in Patients with Metastatic Esophageal Cancer

Schema

1. Cetuximab: Loading 400 mg/m² then 250 mg/m² I.V. Weekly
2. Dasatinib: 240 mg P.O. daily

Response evaluation every 8 weeks

PR or SD

CR

Eight more weeks of treatment then stop

Eight more weeks of treatment then stop

Off Study
Objectives

- Assess 6-month overall survival in previously treated patients with metastatic esophageal cancer given the combination of dasatinib and cetuximab
- Assess ORR in this patient population
- Assess TTP in this patient population
- Determine the toxicity of this drug combination
- Correlative: gene expression and germ-line polymorphisms of EGFR pathway; measure src mutations

Rationale

S0415 demonstrated activity for cetuximab in patients with previously treated esophageal cancer. Src is commonly activated/over-expressed in esophageal cancers, and activation may be mediated through the EGFR pathway. Dual inhibition of the Src pathway (directly through dasatinib and upstream, through cetuximab) may decrease invasiveness, growth, and tumor survival in esophageal cancer.

Statistics

Building on the results from S0415, the addition of dasatinib to cetuximab will be considered to be of interest if the true 6-month OS probability with this treatment is 53%. Sixty-five eligible patients will be accrued to this trial. If the observed 6-month overall survival probability is 46% or greater, this will be considered evidence that this regimen warrants further testing, provided other factors such as toxicity appear favorable. This design has a power of 89% when the true 6-month overall survival probability is 53%, and a significance level of 0.04.

Results and Conclusions

This trial has not yet been activated

S0918: A Phase Ib/II Study of Gemcitabine, Erlotinib, and AMG102 in Patients with Nonmetastatic, Locally Advanced, Pancreatic Adenocarcinoma (Young Investigator project)

Objectives

- Estimate the median overall survival of patients with non-metastatic, unresectable, locally advanced pancreatic adenocarcinoma treated with gemcitabine, erlotinib, and AMG102.
- ORR
- R0 resection rate
- Pathologic response rate
- PFS

Schema

TBD

Rationale

The combination of gemcitabine with erlotinib, an epidermal growth factor tyrosine kinase inhibitor (EGFR-TKI), resulted in a modest increase in 1-year and overall survival in patients with advanced pancreas cancer. Hepatocyte growth factor/scatter factor (HGF/SF) signaling through c-Met plays an important role in proliferation, invasion, metastasis, and angiogenesis in various tumor types. The hypoxic tumor-stromal environment accelerates pancreatic cancer progression via the activation of paracrine HGF/c-Met signaling, and HGF/c-Met expression in patients with pancreatic cancer is associated with worse disease-free survival. Down regulation of c-Met nearly completely inhibited insulin-
like growth factor (IGF-I)-mediated migration and invasion in pancreatic cancer cells in preclinical studies. Activated c-Met also appears to be a marker of primary EGFR-inhibitor and EGFR-TKI resistance. AMG102 is a fully human monoclonal antibody that targets HGF/SF, and it is well-tolerated. We hypothesize that combination therapy with gemcitabine-erlotinib and AMG102 will result in improved median survival in patients with non-metastatic, locally advanced pancreatic cancer.

**Statistical Endpoints**
The study will have a phase Ib/II design. The phase Ib portion will follow a dose de-escalation design: 10 patients will be treated at Dose level 1 = 20 mg/kg. If 3/10 of fewer patients have DLT toxicity, this will be the dose for phase II. If more than 3/10 has DLT, enrollment will stop at this dose and 10 patients will be enrolled at Dose Level 2 (15 mg/kg). Similar dose de-escalation rules will be used at Dose Level 2 and (potentially) at Dose Level 3 (10 mg/kg). For the phase II portion, it is assumed that this therapy will be of no further interest if the true median overall survival is 10 months or less, and of interest if the true median overall survival is 15 months or more. An observed median overall survival of 12.5 months or greater will be considered evidence that this regimen is of interest in locally advanced pancreatic cancer. 75 eligible patients are sufficient (in the phase II portion of the trial) to estimate the probability of a particular toxicity to within +/- 12%. Any toxicity occurring with at least a 5% probability is likely (98%) to be seen at least once. We will explore, in a preliminary fashion, primary tumor molecular biomarkers and their association with treatment outcomes (see Translational Studies section below).

**Results and Conclusions**
This trial has not yet been activated.

**S09-TBD: Phase I/II Clinical Trial of Modified FOLFOX and Everolimus in Patients with Metastatic Pancreatic Cancer (Young Investigator project)**

**Schema**
TBD

**Objectives**
- Part I: Finding a recommended phase II dose for the combination.
- Part II: Overall survival
  - PFS
  - ORR
  - Toxicity profile

**Rationale**
Inhibition of a single transduction pathway is usually not sufficient to significantly inhibit neoplastic growth, due to activation of alternate signaling. The EGF pathway signals through PI3K/Akt, leading to cell proliferation and survival, and this path involves the mammalian target of rapamycin (mTOR), an intracellular serine threonine kinase. The synergistic effect of mTOR and EGFR inhibition has been best described in renal cell carcinoma which has a high frequency of mutations resulting in activation of Akt and tuberous sclerosis complex mutations. By blocking mTOR, this could lead to a shift to the mTOR-GbL-rictor complex promoting an increase in Akt phosphorylation, which activates pro-survival signals.

**Schema**
TBD

**Statistical Endpoints**
This study will initially be in limited institutions, with expected accrual of 12-18 patients in the phase I portion of the trial. The phase II portion of the trial will be initiated Group-wide. Based on previous experience in this disease site, we anticipate accrual of 7-10 patients per month.
Phase I study: Patients will receive mFOLFOX6 and everolimus. There will be 3 everolimus dose levels: 1) 5 mg QOD, 2) 10 mg on Mon, Wed, Fri and 3) 5 mg daily. A minimum of three patients will be evaluated at each dose level and six patients will be evaluated at the recommended dose prior to opening the phase II portion of the trial. Standard 3 + 3 dose-escalation will be used to determine the recommended phase II dosing, utilizing CTCAE 3.0 to assess toxicities. Patients will be considered evaluable for DLT if they are eligible, and if they receive any amount of treatment and experience DLT or complete the first cycle of treatment. Patients who are not evaluable will be replaced. Toxicities will be defined as regimen-related if they are possibly, probably or definitely related to treatment. Responses will be documented. The phase I portion of this trial will include intensive monitoring of adverse events in a minimum of 6 patients. A temporary closure will occur prior to opening this study for the phase II portion in order to assess dose, and to evaluate the safety profile more fully prior to implementation of the phase II trial. Assuming this trial opens to the phase II portion, we will continue to monitor adverse event reporting on a regular basis. Frequency of reporting may be modified depending upon patterns observed in the Phase I portion of the trial.

Phase II study: The primary endpoint for the phase II portion of this trial will be overall survival (OS), with progression-free survival (PFS) as a secondary endpoint. Based on previous studies, median OS is approximately 6 months. Based on a 1-sided type 1 error of 5% and a sample size of 85 eligible patients, and assuming approximately 2 years of accrual and 1 year of follow-up, we will have 81% power to detect an improvement from 6 months to 8 months, and 90% power to detect an improvement to 8.4 months. Assuming 85 eligible patients are accrued to the Phase II portion of this trial, we will be able to estimate the probability of any individual adverse event category to within 11%. Any toxicity with an occurrence rate of at least 5% is highly likely (0.99) to be seen at least once. Because of the potential for rapid accrual, this study will not have a formal two stage stopping rule.

Results and Conclusions

This trial has not yet been activated.

C80702: A Phase III Trial of FOLFOX +/- Celecoxib, Administered for 3 or 6 Months, in Patients with Fully-Resected Stage III or High-Risk Stage II Colon Cancer (co-led with CALGB)

Schema

![Schema Diagram]

GASTROINTESTINAL COMMITTEE

GI- 40
Celecoxib will start at time of first treatment of FOLFOX.

**Objectives**

- Demonstrate an improvement in 3-year PFS for the combination of celecoxib and FOLFOX versus FOLFOX alone in fully resected colon cancer patients
- Compare OS in those given FOLFOX alone versus those given FOLFOX + celecoxib
- To assess differences in cardiovascular-specific events with celecoxib versus placebo in population
- To evaluate the impact of celecoxib on pathways involved in colon carcinogenesis
- Demonstrate non-inferiority for 3 months of adjuvant chemotherapy +/- celecoxib versus 6 months of therapy

**Rationale**

While adjuvant chemotherapy has been demonstrated to improve the disease-free and overall survival in patients with stage III colon cancer, the optimal approach remains to be determined. Important questions that need to be addressed included the duration of treatment and whether the addition of targeted agents will improve survival. It is notable that initially in colon cancer therapy, single agent 5FU was given for 1 year and subsequently it was demonstrated that 6 months provided comparable results and small studies have even found that 3 months of treatment may be reasonable. Given the toxicity and cost of 6 months of combination chemotherapy, it is very important to determine if 3 months of therapy is sufficient. Additionally, COX-2 is often up-regulated in colon cancer. In animal models, COX-1 and/or COX-2 inhibitors reverse tumor growth, especially by anti-angiogenic and pro-apoptotic effects. In animals, aspirin, NSAIDs, and selective COX-2 inhibitors have been shown to increase tumor responsiveness to cytotoxic chemotherapy.

**Statistics**

Trials have already begun in Europe to examine the question of 3 months of therapy, but they are only powered to demonstrate non-inferiority at a 5% detection level. A combined meta-analysis of several similar trials would allow a > 2.5% difference to be ruled out while requiring accrual of only 3000-4000 patients per trial. While the statistics for the duration aspect of this trial are still under development, this sample size would allow a detection of a hazard ratio of 0.75 in favor of celecoxib with 90% power (2-sided α=0.025). The 3-year Kaplan-Meier estimate of DFS under the null hypothesis is 0.70. Assuming the targeted hazard ratio of 0.75, this trial could demonstrate a 3-year DFS of approximately 0.76 under the alternative hypothesis.

**Results and Conclusions**

This trial has not yet been activated.
**S09-TBD: A Phase II Study Prospectively Randomizing Patients with Advanced/Metastatic Gastric Cancer or Gastroesophageal Junction (GE) Junction Cancers, based on the Biomarkers TS and ERCC1**

**Schema**

![Diagram of study schema with arrows indicating control arm FOLFOX, experimental arm with TS level ERCC1, low TS low ERCC1 FOLFOX, high TS high ERCC1 CPT-11/taxotere, control arm 5-FU/Oxaliplatin, experimental arm GENOTYPIC low 5-FU/oxaliplatin, high CPT-11/taxotere.]

**Rationale**

Currently there is no standard regimen for UGI malignancies. Irinotecan and docetaxel in patients with advanced gastric cancers offers a response rate of 46% median time-to-progression of 4.5 months, and overall survival of 8.2 months. There is data regarding potential markers of response to chemotherapeutic treatment with fluorouracil and platins. Thymidylate synthase (TS) catalyzes the methylation of dUMP to dTMP, a step in DNA biosynthesis and a critical target for the fluoropyrimidines. Previous data has shown that gene expression of TS in gastric adenocarcinoma treated with 5-FU had an inverse association with response and survival. ERCC1 (Excision Repair Cross-Complementing 1) plays a role in repair of cisplatin DNA adducts. ERCC1 has also shown a statistically significant relationship to response and survival. Specifically, Shirot and associates showed that gene expression of TS and ERCC1 are associated with response and survival to treatment with 5-FU and oxaliplatin (J Clin Oncol 19:4298-304, 2001). They evaluated 50 patients with stage IV colorectal cancer and found gene expression of ERCC1 and TS independently correlated with outcome to treatment with FOLFOX. Patients with high ERCC1 had lower response rates and median overall survival compared with those with low ERCC1.5. SWOG thus proposes a prospective study randomizing patients based on the genotypic markers TS and ERCC1. The control arm would be vs. an experimental/genotypic arm assigned to 5-FU/oxaliplatin (for low TS, low ERCC1) vs. irinotecan (CPT-11)/docetaxel (for high TS, high ERCC1).

**Objectives**

- To assess response rate
- To assess progression-free survival
• To measure overall survival
• To assess frequency and severity

**Statistical Endpoints**
TBD

**Results and Conclusions**
This trial has not yet been activated.

**SIGNIFICANT ACHIEVEMENTS**

Our major accomplishments during the current award period have been in five general areas:

1. **Conceptualization, Design, Conduct, and/or Analysis of a Wide Variety of GI Cancer Phase III Trials with the Potential to Alter Standard of Care.**

**S0205: Phase III Study Comparing Gemcitabine plus Cetuximab versus Gemcitabine in Patients with Locally Advanced or Metastatic Pancreatic Adenocarcinoma (general description, page GI-13 above)**

S0205 was the Intergroup trial of gemcitabine with or without cetuximab, in the treatment of patients with incurable pancreatic cancers. While S0205 failed to identify benefit from the addition of cetuximab to standard gemcitabine, important consequences have arisen from this study. S0205 required tissue submission and thus established the feasibility of community-wide tissue-based research in pancreas cancer. It also suggested cetuximab (and possibly erlotinib) should not be used in this patient population across the board, without tumor molecular analysis. The CRYSTAL study, among others, showed colorectal cancer patients whose tumors exhibit mutated ras do not benefit from anti-EGFR antibodies, while simultaneously showing those with wild-type ras derived significant clinical benefit. A correlative project, S0205A, may demonstrate similar findings—that a specific patient subpopulation from those with pancreatic cancer will derive benefit from cetuximab treatment, establishing the drug as a useful agent, for the first time, and sparing those who cannot derive benefit from potential treatment-related toxicity.

**S0033: Phase III Study of Standard- versus Higher Dose Imatinib Mesylate in Patients with Incurable GISTs Expressing KIT (general description, page GI-8 above)**

S0033 was the North American phase III trial testing two doses of imatinib mesylate in the treatment of advanced GIST. Derived and conducted by the Sarcoma Committee, the trial was analyzed, published, and built upon by the GI Committee. As discussed above, this trial, in conjunction with an identical parallel-run European phase III trial, firmly established 400 mg of daily imatinib as the standard of care dose in incurable GIST patients. Additionally, S0033 had a strong correlative component, and molecular studies were conducted using paraffin tissue from 394 of the tumors. Neoplastic DNA was analyzed for oncogenic mutations in the imatinib targets KIT and PDGFRA, and the results confirmed earlier phase II data showing that patients whose tumors have a KIT exon 11 mutation enjoy longer progression-free and overall survival than patients whose tumor has another kinase genotype. The higher dose had no additional impact on exon 11-mutant tumors, but tumors with an exon 9 mutation appeared to respond better to the higher dose. These findings corroborated data from the parallel phase III trial conducted in Europe and Australasia, and a meta-analysis of the combined correlative datasets will shortly be published. Thus, S0033 has led to molecularly-targeted, dose-specific therapy for the individual patient, (higher imatinib dosing for exon 9 patients), one of the earliest such trials to do so.
S0502: Phase III Trial of Imatinib Mesylate, plus or minus Bevacizumab, in Patients with Incurable Gastrointestinal Stromal Tumors (general description, page GI-25 above)

This ongoing North American Intergroup phase III trial attempts to determine whether inhibiting angiogenesis, proven to be an important process in the malignant behavior of GIST, will lead to prolonged PFS for advanced disease patients. Important correlative work will explore the association between soluble VEGF, VEGF-D, VEGFR-1, VEGFR-2, angiopoietin-2, PDGFR-AA and PDGFR-BB levels, PET imaging and immunohistochemistry for p16, VEGF and VEGFR, with kinase mutation status and clinical outcomes, as well as explore imatinib pharmacokinetics with single nucleotide polymorphisms involving the ABCG2 and CYP3A4 genes, as well as other genes that are reported to influence the absorption, distribution, metabolism and elimination of imatinib. This trial has the potential to change the standard of care therapy for all untreated GIST patients, the first trial to do so since 2000. More importantly, it may lead to tailoring of therapy for individual patients (imatinib plus bevacizumab for patients whose tumors are highly dependent on angiogenesis; imatinib alone for those whose tumors are not).

CTSU/C80405: A Phase III Trial of Irinotecan/5-FU/Leucovorin or Oxaliplatin/5-FU/Leucovorin with Bevacizumab, or Cetuximab (C225), or with the Combination of Bevacizumab and Cetuximab for Patients with Untreated Metastatic Adenocarcinoma of the Colon or Rectum. (general description, page GI-27 above)

This jointly-coordinated effort between SWOG and CALGB is a phase III trial testing “dealer’s-choice” best chemotherapy, with bevacizumab, cetuximab, or both biologic agents, in colorectal cancer patients with wild-type KRAS. It clearly has the potential to change standard of care therapy for colorectal cancer patients with untreated disease. Additionally, C80405 includes collection of blood, serum and tumor tissues for a comprehensive analysis of biomarkers potentially associated with outcome and toxicities. This will be discussed further in below.

S0518: Phase III Prospective Randomized Comparison of Depot Octreotide Plus Interferon Alpha Versus Depot Octreotide Plus Bevacizumab (NSC #704865) in Advanced, Poor Prognosis Carcinoid Patients (general description, page GI-26 above)

This phase III trial of depot octreotide with either interferon or bevacizumab is the first phase III carcinoid trial patients ever attempted in the Intergroup. S0518 has the potential to set a new regimen as standard of care therapy for patients with poor-prognosis carcinoid, the first such change in years or even decades. Additionally, the study will investigate the potential prognostic and predictive values of VEGF expression in relation to progression-free survival. It will assess and compare the prognostic and predictive value of the combination of In-111 pentetreotide somatostatin-receptor scintigraphy (SRS) and CT versus CT in relation to PFS, overall survival, and TTF. The correlative work is hypothesis-generating and may lead to protocols better individualizing therapy, as well as studies to determine the best or most cost-effective imaging utilized in determining response.

SWOG 0600: Phase III Trial of Irinotecan-Based Chemotherapy plus Cetuximab (NSC-714692) versus Irinotecan-Based Chemotherapy plus Bevacizumab (NSC-704865) as Second-line Therapy for Patients with Metastatic Colorectal Cancer who have Progressed on Bevacizumab with either FOLFOX, OPTIMOX or XELOX plus Bevacizumab. (General description, page GI- 28 above)

The most widely used American first-line therapy for advanced colorectal cancer at present is FOLFOX with bevacizumab. Irinotecan alone or in combination with a fluoropyrimidine is generally used as second–line treatment, sometimes but not always combined with cetuximab. One very important question at present is whether the continued use of bevacizumab after progression improves long-term survival. It has been argued that bevacizumab will continue to assist in normalizing tumor vasculature,
enhance the delivery of the new chemotherapy to the tumor via the blood stream and hence improve the outcome of treatment. On the other, hand the continuation of bevacizumab may add to toxicity and certainly increases the cost of therapy a great deal. 0600 compares bevacizumab-continuation to an alternate strategy, adding an anti-EGFR antibody (cetuximab) to irinotecan-based chemotherapy. Since this study, like CTSU/C80405 described above, involves the use of cetuximab, this study was modified to only include patients who are wild type \textit{K-ras}. Because of the extensive correlative work in C80405, SWOG’s first-line study involving the same drugs, plus the need for strong and rapid accrual, 0600 is one of the few recent SWOG trials to be conducted without its own correlative component, as specifically discussed with the NCI.

\begin{itemize}
\item \textbf{(2) The conceptualization, design, conduct, and analysis of 12 innovative pilot phase I and II GI malignancy trials examining novel targeted therapeutics or regimens.}
\end{itemize}

Over the prior grant period the Gastrointestinal Committee has conducted numerous innovative pilot trials exploring new agents and combined modality treatments for patients with GI cancers. Examples of such studies include:

\begin{itemize}
\item \textbf{Novel Single Agents:}
\item \textbf{S0107: A Phase II Trial of Epothilone B Analogue BMS-247550 (NSC #710428) Every 21 Days in Patients with Advanced Pancreas Cancer}

This was a phase II trial of epothilone B analogue ixabepilone in patients with advanced pancreas cancer with the primary endpoint of six-month survival rate. Sixty-two patients were enrolled and of the 60 eligible patients estimated 6-month survival was 60\% (95\% CI 48-72\%) with a median survival of 7.2 months. Of the patients with measurable disease the objective response rate was 9\%. Major toxicities were related to myelosuppression, upper GI toxicities and neuropathy. It was concluded that the activity of ixabepilone as single agent was encouraging and probably comparable to that of gemcitabine.

\item \textbf{S0127: A Phase II Study of OSI-774 (NSC #718781) in Unresectable or Metastatic Adenocarcinoma of the Stomach and Gastroesophageal Junction}

This phase II study was the first cooperative group trial that evaluated the blockade of the EGFR pathway in patients with advanced stomach or gastroesophageal cancer. OSI-774 is an oral tyrosine kinase inhibitor that was tested as a single agent in this population of patients. Interestingly, this study showed a difference in the potential of activity of EGFR blockade in the GE junction and stomach, the first time this had been reported. Further, several molecular correlates were proposed and this evaluation was the first time no somatic mutation was demonstrated in evaluation of patients with stomach and GE junction adenocarcinoma. Other correlates were also evaluated, including EGFR, IF, TGF alpha, PAKT, although the molecular correlates were not predictive of response. This study provided the justification for future studies in which to incorporate EGFR blockade, such as S0413 and S0415.

\item \textbf{SWOG 0336: A Phase II Trial of Depsipeptide (NSC-630176) in Colorectal Cancer Patients Who Have Received Either One or Two Prior Chemotherapy Regimens for Metastatic or Locally Advanced, Unresectable Disease.}

Approximately 60\% of colorectal cancers have ras gene mutations. Depsipeptide (a product of \textit{Chromobacterium violaceum}) is able to induce reversion of the ras transformed phenotype to normal. It is also a potent inhibitor of the enzyme histone deacetylase. Depsipeptide has shown potent antitumor effects \textit{in vitro} against tumor cell lines and \textit{in vivo} in murine and human tumor xenograft model. This was a phase II trial testing depsipeptide in the treatment of refractory advanced colorectal cancer. Twenty-five patients were accrued between 4/04 and 9/05. No objective responses were observed. SWOG
concluded that depsipeptide at this dose and schedule was considered to be ineffective in the treatment of patients with metastatic colorectal cancer who had failed prior chemotherapy.

**S0413: Phase II Study of GW572016 (NSC-727989) as First Line Therapy in Patients with Advanced or Metastatic Gastric Cancer**

GW572016 (lapatinib) is an oral tyrosine kinase inhibitor of EGFR1 and EGFR2 (HER2). This phase II study evaluated single agent lapatinib in patients with advanced stomach cancer, demonstrating a response rate of 13% and stable disease rate of 20%. Although this response rate was modest, markers associated with median survival were identified in the correlative sub-studies (Her2 and Il8). This is the first time molecular markers were associated with efficacy to lapatinib.

**S0415: Phase II Study of Cetuximab as Second-Line Therapy in Metastatic Esophageal Cancer**

This phase II clinical trial was one of the first attempts for a cooperative group to define a role for a targeted agent against esophageal cancer. Given that this regimen was associated with a 36% 6-month survival rate, and that it was well tolerated, trials combining cetuximab with cytotoxic chemotherapy in metastatic esophageal cancer appear reasonable. SWOG is now initiating a phase II trial using combination chemotherapy with FOLFOX plus cetuximab as first-line therapy for these patients. Further, the SWOG cetuximab data have been used by ECOG to justify the use of cetuximab in the neoadjuvant setting for esophageal cancer. ECOG 2205 is a study that combines 5-FU/Oxaliplatin and cetuximab as neoadjuvant therapy for esophageal cancer. SWOG will collaborate with ECOG to complete rapid accrual.

**SWOG-0514: A Phase II Study of Sorafenib as a Single Agent in patients with Unresectable or Metastatic Gallbladder Cancer or Cholangiocarcinoma**

This phase II trial was designed based on emerging data regarding the molecular carcinogenesis of biliary cancers (role of BRAF mutations). The study utilized sorafenib, a drug active against HCC, as a single agent in patients with unresectable or metastatic gallbladder carcinoma and cholangiocarcinoma. The study closed after the first stage of accrual (36 patients) due to failure to meet its response end point. Although the study failed to meet its primary endpoint, the OS and PFS were comparable to results reported with chemotherapy combinations. Alternative funding is being pursued to complete planned correlative studies that include the evaluation of B-raf mutational status, VEGF serum level and VEGFR2 gene expression.

**Novel Combined Modality Regimens**

**S0356: Phase II Study of Oxaliplatin Plus Protracted Infusion 5-Fluorouracil and Radiation for Potentially Curable Esophageal Cancer**

This phase II clinical trial evaluated 5-FU/oxaliplatin and radiation as neoadjuvant treatment in patients with potentially resectable esophageal cancer. The primary endpoint is pathologic complete response rate. The study also allows for eloquent molecular correlates with biopsies prior to treatment and after one cycle of therapy with evaluation of markers of response and survival to 5-FU and oxaliplatin, including gene expression of TS, ERCC1, and XPA, as well as genetic polymorphisms of TS and ERCC1. This study is to close in August and has completed accrual 2 years before competing trials from other cooperative groups. The goal ultimately is to determine if a molecular profile can be defined for those patients with a pCR, conversely, if a molecular profile can be defined for those without evident response to preoperative therapy. This study will provide the backbone to the neoadjuvant study to be done by ECOG in their study E2205 – A phase II study to measure response rate and toxicity of neoadjuvant chemoradiotherapy with oxaliplatin and infusional 5-FU plus cetuximab followed by post-operative docetaxel and cetuximab in patients with operable...
S0727: A Phase I and Randomized Phase II Trial of Gemcitabine plus Erlotinib (NSC-71817 + IMC-A12 (NSC-742460) versus Gemcitabine plus Erlotinib as First Line Treatment in Patients with Metastatic Pancreatic Cancer

This is a randomized Phase I/II study of gemcitabine and erlotinib with or without the anti-IGF-1R monoclonal antibody IMC-A12 in patients with metastatic pancreas cancer who are not previously treated with chemotherapy for metastatic disease. Signaling through the IGF-1R receptor has been implicated in cell proliferation, survival and drug resistance including EGFR blockade. After determination of an appropriate dose for IMC-A12 and efficacy of the overall regimen, correlative studies will explore relationships between germ line mutations in K-Ras and PTEN and EGFR/PI3K gene expression levels and PFS/OS.

(3) Complete reorganization of the Committee’s structure, to enhance our multidisciplinary approach to GI malignancy research.

Since the last site visit there have been major changes in the Committee, including new overall leadership (Blanke) and recruitment of outside, internationally recognized experts in GI Oncology into Subcommittee leadership positions (Corless, Billingsley). The Vice-Chair (Lenz) and Head Biostatistician (Benedetti) remain the same.

The Committee leadership recognized efforts to identify new targets for antineoplastic therapy based on the evolving understanding of the molecular biology of GI cancers have become an increasingly important focus in clinical oncology research. Several recurring themes were seen across the GI sites, and this led to a desire to coordinate central ideas by emphasizing the role of the Translational Medicine Subcommittee. At the same time, the diverse nature of GI neoplasms, and increasing recognition of the importance of having experts in medical, surgical, and radiation oncology capable of mounting a multi-pronged research effort, was felt to be of paramount importance. These factors led to a complete restructuring of the GI Committee. Additionally, young investigators were given a more prominent role, with significant mentoring by previous GI Committee leadership.

Five subcommittees representing anatomic GI sites were established, each run by Medical Oncology co-chairs, as well as a Surgical Liaison (Surgical co-chair). Pancreas and hepato-biliary were separated because of the success the GI committee has had in designing and accruing to biliary studies. Disease-oriented subcommittees now include Gastroesophageal Cancer (Drs. Syma Iqbal, Larry Leichman, and Scott Hundahl), Pancreatic Cancer (Drs. Philip Philip, and Andrew Lowy), Hepatobiliary Cancer (Drs. Melanie Thomas, Anthony El-Khoueiry, and Syed Ahmad) and Colorectal Cancer (Drs. Philip Gold, Tony Shields, and Kevin Billingsley). Indeed, radiation and surgical oncology experts are participating earlier and more regularly in protocol development because of new Subcommittee structure.

The Translational Medicine Subcommittee (Drs. Heinz Lenz and Christopher Corless) strongly supports the objective of having translational research attached to all major GI protocols. The Drug Development Subcommittee (Drs. Ramesh Ramanathan and Robert Whitehead) actively recruits new agents from both the NCI and pharma, often exploring avenues not pursued by the disease-oriented committee personnel, and allowing similar protocols with similar correlative sub-studies to be performed across disease sites. Additionally, recognizing the importance of dual-modality therapy in a number of GI neoplasms, Dr. Lisa Kachnic was appointed Radiation Oncology Liaison to the entire GI Committee. As such, she helps formulate independent RT-related research questions, as well as to integrate RT techniques into multimodality protocols. Active subcommittee chairs and liaisons, as well as former senior members, serve as members of the GI Core Committee, which is the executive body responsible for approving new protocols, shaping the overall vision of the Committee, and which decides how to best participate in Intergroup efforts.

Specific clinical and translational research goals and the generation and prioritization of new protocols are set through twice-yearly general committee meetings, twice-yearly Core committee meetings, and at
least monthly teleconferences, coordinated by the Gastrointestinal Cancer Committee leadership. Monthly calls are used to discuss issues or problems with any individual protocol, as well as to feature one site in the GI tract, to discuss the GI Committee’s “vision” for research in that anatomic area. Discussion of overarching themes or principles that may extend to multiple disease sites, and make the group more cohesive are emphasized, particularly in terms of translational projects.

At general meetings the entire Committee’s membership is encouraged to increase participation in research activities, engaging a broad-based group of clinical and translational scientists in the design and execution of individual trials and the entire SWOG organization’s scientific agenda. Thus, the Gastrointestinal Cancer Committee remains particularly well-positioned to take full advantage of available opportunities in GI cancer research during the next grant cycle.

4. Enhancement of the mentoring of young investigators, leading to effective training of the next generation of GI cancer researchers.

Identifying, training, and subsequently mentoring the next generation of clinical and translational researchers to carry on and improve progress against GI malignancies is essential. Toward this end, the Gastrointestinal Cancer Committee has made a major commitment to the training and mentoring of new investigators. The Gastrointestinal Cancer Steering Committee has prioritized identification of fellows and junior faculty investigators with interests in GI malignancies and has facilitated access to clinical trials training and investigator roles in phase II trials. This has borne fruit in a number of ways; in addition to generating several recently activated protocols, many junior members have subsequently gone on to leadership positions in the GI Committee.

Of special note, the GI committee has taken advantage of the Southwest Oncology Group Young Investigators Program (described in depth in the Administrative section of this grant) by mentoring a number of new investigators. The young investigators who were trained through this program are listed below, along with their protocols.

Syed Ahmad, M.D., April 2004. **S0425**: Neoadjuvant Chemoradiation Therapy with Oxaliplatin and Capecitabine for Patients with Surgically Resectable Gastric Cancer: A Pilot Phase II Trial with Molecular Correlates.

Anthony B. El-Khoueiry, M.D., Sept 2004. **S0514**: Phase II Study of BAY 43-9006 (NSC #724772) as Single Agent in Unresectable or Metastatic Gallbladder Carcinoma and Cholangiocarcinoma.

Cathy Eng, M.D., Sept 2005. **S0531**: A Phase II Study of Capecitabine / Oxaliplatin /Cetuximab with Concomitant Radiotherapy, XELOX-E/XRT, in Locally Advanced Squamous Cell Carcinoma of the Anal Canal (suspended because of budget constraints)

John Strother, M.D., Sept 2005. **S0527**: Phase II Trial of Neoadjuvant Gemcitabine plus Oxaliplatin (GEMOX) and Subsequent Cetuximab-Enhanced Radiotherapy, Pancreatoduodenectomy, and Adjuvant GEMOX in Patients with Potentially Resectable Adenocarcinoma of the Pancreatic Head. (suspended because of budget constraints)

Nestor Esnaola, M.D., M.P.H., Sept 2006. Phase II Study of Neoadjuvant Chemoradiation with Standard Dose Gemcitabine and Limited Field Radiotherapy in Patients with Borderline Resectable, Locally Advanced Pancreatic Head Adenocarcinoma. (Project dropped; however, Dr. Esnaola is working on a new capsule.)

Vincent Chung, M.D., Sept 2007. Randomized Phase II Study to Evaluate the Efficacy and Safety of ZD6474 at Two Different Doses in Patients with Refractory Pancreatic Cancer. (Project dropped;
however, Dr. Chung is working on a new capsule.)

Richard Kim, M.D., Sept 2008. **Phase II Trial of Everolimus and Cetuximab in Metastatic Colon Cancer Patients with K-ras Mutations Following Progression of First-Line or Second-Line Therapy.**

Additionally, four Young Investigators have become GI Subcommittee Heads. *(Iqbal, Thomas, El-Khoueiry, and Ahmad)*. Two (Iqbal and Thomas) participated in the course prior to this grant cycle but were recently appointed.

*(5)* **Widespread placement of GI Committee members in NCI-based leadership positions, positioning SWOG to help shape long-term national anti-cancer policy.**

The GI Committee recognizes and acknowledges the effectiveness of the new structure which has evolved from the old GI Intergroup (now the NCI-designated GI Steering Committee, with the related disease-oriented Task Forces). Many GI committee members are recognized experts in their niche areas, and they have become involved at multiple levels within the NCI-structure, as listed below:

**GI Steering Committee Membership**

Charles Blanke

Heinz-Josef Lenz

Jacqueline Benedetti

**Task Force Leadership:**

Andrew Lowy: Co-chair, Pancreatic Cancer Task Force

James Yao: Co-chair, Neuroendocrine Cancer Task Force

Charles Blanke: Chair, GIST Task Force

**NCI State-of-the-Science Leadership:**

Philip Philip: Conference chair, SOTS meeting in pancreatic cancer, November 2007

Melanie Thomas: Conference chair, SOTS meeting in hepatobiliary cancer. December 2008

James Yao: Conference Chair, SOTS meeting in neuroendocrine cancer. 2009

**6. Extensive collaboration with other SWOG committees and Cooperative Groups, to more rapidly and fully answer important national questions in GI malignancy research and care.** The Translational Medicine Subcommittee has extensively collaborated with the SWOG Lung and GU Committees, as well as ECOG. Besides strongly supporting other Cooperative group trials through CTSU accruals, several disease-oriented GI Subcommittees have also actively collaborated with other groups to develop and co-lead phase II and III clinical and translational protocols. Examples detailed in other sections of the grant include:
C80405: Phase III trial of FOLFOX or FOLFIRI chemotherapy, with bevacizumab, cetuximab, or both, in patients with untreated incurable metastatic colorectal cancer)-CALGB

S0600 (iBET): Phase III trial of irinotecan-based chemotherapy, with cetuximab, plus or minus bevacizumab, as second-line therapy in patients with metastatic colorectal cancer failing bevacizumab -NCCTG

R0848: Gemcitabine, with and without Erlotinib, Followed by a Second Randomization, with and without Chemoradiation, as Adjuvant Treatment for Pancreatic Head Cancer: A Phase III RTOG/SWOG/NCIC/EORTC Study

C80702: A Phase III Trial of FOLFOX +/- Celecoxib, Administered for 3 or 6 Months, in Patients with Fully-Resected Stage III or High-Risk Stage II Colon Cancer-CALGB

Finally, the Translational Medicine Subcommittee has established formal communication and collaboration with groups outside of North America, including the Japanese Society of Clinical Oncology, the Medical Research Council, and the European Organization for the Research and Treatment of Cancer.

7. Development of new technologies and identification of new molecular markers associated with outcome in GI malignancies, with incorporation of correlative sub-studies into the majority of GI Committee trials.

The Translational Medicine Subcommittee has been very productive over the last funding period, initially generating preliminary marker data, later tested and validated in prospective studies. The strength and impact the Translational Medicine Subcommittee has had is reflected in the tissue and blood/serum collection on GI protocols. A wide variety, and large number of specimens have been systematically collected over the grant cycle, with some representing the largest known assembly from a specific disease type (e.g., pancreatic cancer tissue from metastatic disease) (Table 1).

Table 1: Collection of Tissue, Blood, Plasma and Serum Samples in SWOG Trials.

<table>
<thead>
<tr>
<th></th>
<th>Whole Blood</th>
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<td><strong>294</strong></td>
<td><strong>95</strong></td>
<td><strong>960</strong></td>
</tr>
</tbody>
</table>

The Translational Medicine Subcommittee has extensively collaborated with groups outside of the GI Committee. Specifically, based on expertise in pharmacogenomics of UGT-1A1 and DNA repair, Dr. Lenz was a co-PI of the Strategic Program to Evaluate Cancer Signatures Program in...
lung cancer (PI David Carbone), helping to determine the clinical significance of germ-line polymorphisms of DNA repair and metabolizing genes in the CPT-11 pathway. Additionally, novel polymorphisms were demonstrated to be associated with GI toxicity.\textsuperscript{9,10} In further collaboration with SWOG Lung Committee and Japanese investigators, the frequency of germ-line polymorphisms in DNA repair genes such as ERCC-1, XPD and others was shown to be significantly different between populations, giving a possible explanation for the difference in toxicities and efficacies seen in NSCLC using CPT-11/CDDP or CDDP/etoposide. Based on these interesting experiences, the Translational Medicine Subcommittee more formally established collaborations with the Japanese Society of Clinical Oncology (Baku, Nagashima) and European Organization for the Research and Treatment of Cancer (Van Cutsem, Tejpar) to identify differences among different ethnic population as well as to have the opportunity to validate and confirm molecular findings in different patient populations and to carry out meaningful GI malignancy research.

SWOG GI Translational Medicine Subcommittee members have been successful in pursuing independent funding. Dr. Lenz ran an R01 investigating molecular determinants of recurrence in resected gastric cancer patients randomized to observation versus chemoRT, and he recently received an R01 to identify molecular markers predicting rectal cancer recurrence. Two young investigators received NCI/CTEP TRF funding for phase II protocols done during the grant cycle (S0413Dr. Iqbal and S0514-Dr. El-Khoueiry).

Other selected examples of Translational Medicine Subcommittee achievements are detailed below.

**S0030: Phase II Protocol for Assessment of Capecitabine for Advanced Colorectal Cancer in Patients Aged 70 Years and Older**

R01 funding for this project reflected the strong collaboration among the Disease Committees (GU, breast, doing similar trials within their disease sites) within SWOG and took advantage of the high-level of molecular expertise within SWOG. The primary objective of this study was to assess the feasibility of enrolling patients aged 70 years or older with advanced colorectal cancer to a structured phase II trial that included pharmacokinetic sampling, while also exploring, at a preliminary level, the feasibility of studying genetic polymorphisms and gene expression levels of enzymes involved in drug metabolism and resistance to capecitabine (including thymidylate synthase [TS], dihydropyrimidine dehydrogenase [DPD] and thymidylate phosphorylase) in standard and elderly population groups. Interesting differences between patients older than 70 compared to patients younger than 60 were demonstrated. PK and clearance data show statistically significant lower clearance and higher AUC in patients older that 70 with metastatic colon cancer treated with capecitabine. PK data analysis, including the metabolites of the 5-FU pathway, is still being undertaken.
S0127: A Phase II Study of OSI-774 (NSC #718781) in Unresectable or Metastatic Adenocarcinoma of the Stomach and Gastroesophageal Junction

This phase II study of erlotinib in GE junction and gastric cancer patients was the first to study EGFR inhibitors in this patient population. Dr. Dragovich, in collaboration with Dr. Fenoglio-Preisser, hypothesized that mutations of EGFR and EGFR amplification were associated with outcome. Their data were the first showing that there were no somatic mutations in EGFR exons 18, 19 and 21 and that neither EGFR expression, TGF-alpha nor pAKT was associated with results. EGFR amplification was demonstrated in these patient populations.

S0356: Phase II Study of Oxaliplatin plus Protracted Infusion 5-Fluorouracil and Radiation for Potentially Curable Esophageal Cancer

This is a recently completed phase II study using oxaliplatin and 5-FU in combination with radiation therapy in respectable esophageal cancer patients. The endpoint is complete pathological response. The correlative component will test whether gene expression levels of TS and ERCC-1 will be able to predict patients achieving a complete pathological response. In addition the clinical significance of down-regulation of ERCC-1 with chemoradiation will be tested in this patient population. SWOG-developed technology will be utilized to measure intratumoral gene expression levels, using laser capture microdissection based on Taqman based technology.

S0413: A Phase II Study of GW572016 (NSC-727989) as First Line Therapy in Patients with Advanced or Metastatic Gastric Cancer

This phase II study of lapatinib in advanced gastric cancer patients was based on preliminary data from S9008 showing about 20% of patients have her2 amplification. It included exploratory correlative studies such as assessment of germ-line polymorphisms and intratumoral gene expression levels. Tumor tissues were successfully collected from 35 of 43 patients and blood samples from 42 of 43 patients. A significant association of her2 and II-8 gene expression was shown to be associated with median survival in this patient population, and also suggested a potential association between survival and germ line polymorphisms of II-8 and II8 expression. These exploratory results are the first to identify potential molecular markers associated with clinical outcome in patients treated with lapatinib.
S0415 – Phase II Trial of Cetuximab as Second Line Therapy in Metastatic Esophageal Cancer

This phase II study tested the efficacy of cetuximab in refractory metastatic esophageal cancer. Esophageal adenocarcinoma over-expresses the epidermal growth factor receptor (EGFR), providing the rationale for examining the use of the anti-EGFR monoclonal antibody cetuximab. Tumor tissue was collected for correlative studies, and SWOG collected adequate tissue for analysis in 42/55 patients. Germ-line polymorphisms in genes involved in the EGFR and VEGF pathway (EGFR, EGF, Il-8, COX-2, VEGF, cyclin D, NRP) were studied. Possibly due to low overall efficacy and small samples size, no associations with response, overall survival, time to progression, time to treatment failure or toxicity were found. One kras mutation out of 42 pts (2%) was detected, thereby showing for the first time that kras mutational status does not play a major role in resistance to EGFR inhibitors in esophageal cancer.

C80405: A Phase III Trial of Irinotecan/5-FU/Leucovorin or Oxaliplatin/5-FU/Leucovorin with Bevacizumab, or Cetuximab (C225), or with the Combination of Bevacizumab and Cetuximab for Patients with Untreated Metastatic Adenocarcinoma of the Colon or Rectum

C80405 includes collection of blood, serum and tumor tissues for a comprehensive analysis of biomarkers potentially associated with outcome and toxicities. SWOG is responsible for the banking of specimens from this study, as well as leading the correlative effort. Preliminary data from SWOG investigators previously showed, in metastatic colorectal cancer treated with FOLFOX/bevacizumab, those germ-line polymorphisms of ICAM, GRP78 and NFK\(\kappa\) were associated with response and progression free survival. However, to date, no predictive or prognostic molecular markers have been identified and validated in association with VEGF-targeted therapy. SWOG investigators evaluated polymorphisms of genes involved in the angiogenesis, cell proliferation, and cell-cell or cell-matrix interaction as potential predictors of clinical outcome in patients with mCRC who received bevacizumab (BV) as part of their frontline therapy, including: VEGF, VEGF receptor 2, neuropilin 1, epidermal growth factor receptor, Interleukin 6 and 8, adrenomedullin, leptin, fibroblast growth factor receptor 4, tissue...
factor, matrix metalloproteinases 2, 7, 9, intercellular adhesion molecule-1 (ICAM-1), glucose related protein 78 (GRP78), and nuclear factor kappa b (NFkB). They were able to show significant association of polymorphisms within the CA-repeat sequence at locus 4q23-24 of the NFkB gene with progression free survival (Fig. X). Pioneering work done pre-SWOG by SWOG investigators demonstrated the single nucleotide polymorphisms within the genes of ICAM-1 (Figure Y) and GRP78 (Figure Z) were significantly associated with therapeutic response.

Hypotheses developed from these exploratory analyses will be further tested in the C80405 study.
S0518: Phase III Prospective Randomized Comparison of Depot Octreotide Plus Interferon Alpha versus Depot Octreotide plus Bevacizumab (NSC #704865) in Advanced, Poor Prognosis Carcinoid Patients

This phase III trial of depot octreotide with either interferon or bevacizumab has the potential to set a new regimen as standard of care therapy for poor-prognosis carcinoid. Additionally, the study will also determine the prognostic and predictive values of VEGF expression in relation to PFS and will assess and compare the prognostic and predictive value of the combination of In-111 pentetreotide somatostatin-receptor scintigraphy (SRS) and CT versus CT in relation to PFS. It will also assess and compare the prognostic and predictive value of the combination of SRS and CT versus CT in relation to overall survival and TTF. The correlative work is hypothesis-generating and may lead to protocols better individualizing therapy, as well as studies to determine the best or most cost-effective imaging for response.

VISION

Encompassing Vision

The Gastrointestinal Committee is a multidisciplinary research group comprised of clinical and translational investigators representing a variety of specialties, including Medical Oncology, Surgical Oncology, Radiation Oncology, Pathology, Gastroenterology, and Biostatistics. Areas of research expertise include clinical research trial design and biostatistics, experimental therapeutics, molecular therapeutics, pharmacogenomics, and molecular pathology. The principal mission of this committee is to develop new clinical and translational medical knowledge that will markedly decrease morbidity and mortality from GI malignancies, both in North America, and worldwide. Previously research efforts were mostly empiric, and some progress was made (e.g., SWOG-9008: A Phase III Intergroup Trial of Adjuvant Chemoradiation after Gastric Cancer Resection). However, the Committee’s future approach to GI cancer research will involve greater use of the SWOG GI Cancer Correlative Sciences Subcommittee, based on its evolving understanding of the molecular basis of GI neoplasms, to work toward its goal of individualizing cancer therapy. In general, the GI Committee will:

1) Take the lead in identifying new targets and potential new drugs for therapeutic intervention, with special strengths in neuroendocrine cancers, GIST, colon cancer, and esophageal cancer;
2) Test drugs aimed at those targets in phase II, then III settings;
3) Continue to develop programs of individualized therapy, ultimately to be based on molecular biology and not disease site;
4) Develop and evaluate novel therapeutic approaches to prevent GI neoplasms in high-risk and other defined patient populations.
5) Contribute as both leader and active participant in Intergroup efforts.

Elements 1 and 2 have been previously discussed. Below are listed additional plans and goals by Subcommittee, as well as a more detailed description of elements 3-5.

Gastroesophageal Subcommittee:

The UGI Subcommittee has extensively utilized the expertise of the Translational Medicine Subcommittee, incorporating molecular correlates into all trials being done. One of the major goals of the UGI Subcommittee is to initiate a prospective, marker-driven, randomized study for patients with gastric cancer, to test the hypothesis and utility of knowing these markers prospectively. Additionally, SWOG continues to work with the UGI Task Force in designing the next generation of phase III trials, particularly assessing which concepts from SWOG investigators best complement the programs of
the other cooperative groups and helping to establish new standards of cancer practice for these tumors. For example, the Upper GI Subcommittee recognizes the potential limitations (usually accrual) of pursuing neoadjuvant studies in upper GI tumors. Nevertheless, SWOG has been on the forefront with S0356, creating the backbone of therapy (5FU/oxaliplatin) for the development of the current Intergroup trial led by ECOG, adding the novel therapeutic cetuximab to that regimen. Future trials within SWOG will build further on these studies by looking for new targets, such as adding the Src inhibitor dasatinib to cetuximab in second line esophageal cancer patients. Ultimately, the evaluation of the molecular correlates done with each of their studies expands the platform which to build further treatments and may eventually allow for tailored treatment in these diseases in which combinations of chemotherapy have not significantly changed outcome thus far.

Pancreatic Subcommittee:

In general, the Pancreatic Subcommittee plans to test combinations of targeted therapies in pancreatic cancer, after screening for single agent activity of biologic agents in patients with gemcitabine-refractory disease. Building upon the success of S0205, the members of this Subcommittee wish to enhance the range of correlative science that can be performed at the community level and in certain selected cancer centers. Finally they plan to utilize the adjuvant model to better understand biology and to develop predictive biomarkers. Specific pancreatic cancer future projects include a young-investigator award trial of FOLFOX and everolimus in gemcitabine-refractory metastatic disease, and a Young Investigator trial of gemcitabine, erlotinib, and AMG 102 in locally advanced disease.

Hepatobiliary Subcommittee:

The Hepatobiliary Subcommittee was recently established as an independent subcommittee within the SWOG GI Committee, whereas it had been combined with the Pancreatic Subcommittee previously. This decision was based on several factors, including the rising incidence of hepatocellular carcinoma and intra-hepatic cholangiocarcinoma, the already-delivered promise of improved treatment options with molecularly targeted therapies such as sorafenib in hepatocellular carcinoma, the success of SWOG at rapidly completing phase II studies in biliary cancers, and the commitment to play a future, active role starting at the level of the Hepatobiliary Task Force. More specifically, the promising survival results noted with single agent sorafenib in biliary cancers in SWOG 0514 have provided the impetus for planning a phase II study of the combination of sorafenib and erlotinib; S0809 is a planned adjuvant study in patients with resected extra-hepatic cholangiocarcinoma, partly building upon S0202 which evaluated the efficacy of gemcitabine and capecitabine in patients with metastatic and unresectable biliary cancers. The Subcommittee is also considering options for advanced hepatocellular carcinoma who have failed sorafenib, including the usage of C-met versus mTor inhibitors versus multi-targeted inhibitors of both VEGF and EGFR pathways.

Colorectal Subcommittee:

The Colorectal Subcommittee has been successful in opening phase III trials possessing the potential to alter standard of care for the general population with advanced colorectal cancer (C80405, S0600). Plans are well underway to perform an adjuvant phase III study testing duration of chemobiologic therapy in patients who have been fully resected but who remain at high risk of recurrence (see Section XXX above). However, the overarching goal of the subcommittee is to employ biomarkers to understand and subsequently predict the efficacy of such chemotherapeutic and biologic agents in subgroups of patients, so therapy can be individualized. The recently reported data regarding the lack of efficacy of cetuximab in k-ras mutated colorectal tumors has required a reworking of the study designs for both C80405 and S0600 to accommodate knowledge of patient k-ras status. In addition, k-ras testing was incorporated into the design of SWOG 0713, making it one of the first cooperative group trials to go forward utilizing cetuximab in an “enriched” population of patient with rectal cancer. This will also allow physicians to bypass the use of agents that may be toxic and expensive but which have a very low likelihood of providing any benefits. The correlative work associated with C80405 has provided the infrastructure to
develop a trial that would critically test the question of whether better patient outcomes can be obtained by assigning therapy based on the molecular profile of the individual patient's cancer. The Colon Subcommittee would first need to test feasibility, assess the ability to establish a good link to institutional pathologists and to obtain sufficiently rapid submission of required specimens. Future studies and infrastructure enhancements to conduct group-wide prospective and randomized translational clinical trials will be determined using the information generated by this feasibility trial.

Translational Medicine Subcommittee:

This Subcommittee has already started to collaborate on the design of prospective randomized pharmacogenomic driven studies which allow potential cross validation and confirmation of markers in different treatment settings, by having comparable eligibility criteria across trials, as well as standardization of technologies. Members believe taking advantage of inter-country ethnic diversity as well as tumor heterogeneity will increase the potential to find differences in multiple patient populations, which will lead to individualizing therapy within the United States. Based on exploratory retrospective studies generated from SWOG investigators, two prospective trials using molecular markers to assign therapy are in development. For colon cancer, SWOG is planning to gene expression levels of ERCC-1 to assign presumed best chemotherapy (FOLFOX those with low levels or FOLFIRI for high ERCC-1) and to use k-ras status and expression of EGFR ligands to assign a targeted therapy (cetuximab for those likely to respond and bevacizumab for resistant patients). This four arm phase II study will explore the feasibility of using multiple genetic tests to individualize treatment for each patient. The success of such a study should lead to further phase III studies exploring such selection methods as new approaches to directed therapy are developed. Additional future goals a similar concept study in UGI malignancy and using the group’s molecular expertise to serve as the basis for an R01 in gastric cancer focusing on DNA methylation and the folate enzymes, and an R01 in pancreas cancer to identify a subpopulation who may benefit from EGFR inhibitors. In collaboration with CALGB, multiple grant opportunities may arise from the C80405 study. The laboratory network within SWOG will expand to include the MD Anderson group, focusing on germ-line polymorphisms in pancreas cancer, as well as Dr. Hamilton from ECOG and Dr. Ulrich from the Fred Hutchinson Cancer Center, studying colon cancer. Development of international collaborations driven by molecular markers as discussed.

Additional important Translational Medicine Subcommittee projects include the following:

**S0205A: Predictive and Prognostic Value of Tumor K-Ras Mutation Status, Amphiregulin and Epiregulin and gene expression levels and germ-line polymorphisms involved in the EGFR and gemcitabine pathway in Advanced Pancreas Cancer: A Study of Tissues from SWOG Protocol 0205**

In SWOG 0205, specimens were available for 702 patients, and were adequate to assess EGFR by immunohistochemistry in 595. Of these, 547 (92%) were positive for EGFR. The median survival in this EGFR positive subset was 6 months in both treatment arms (hazard ratio 0.99, 95% CI .83-1.18, p=0.46). The Subcommittee plans to generate data on KRAS, EGFR ligands and genes in the VEGF pathway, to determine their clinical significance. Pancreas cancer is known to have about 90% k- or h-ras mutations, which could be associated with resistance to EGFR inhibitors based on the data recently published in patients with colorectal cancer. The working hypothesis is that only patients with wild-type KRAS will benefit from cetuximab therapy. Additionally, the EGFR ligands heregulin β1, amphiregulin and epiereguin can affect EGFR targeted therapy and might therefore of particular importance in predicting therapeutic response to EGFR-targeted therapy in cancer patients.

Data from a retrospective study by SWOG investigators suggest that gene expression levels or genomic polymorphisms of genes involved in EGFR and gemcitabine metabolic pathway are associated with clinical outcome in patients with colorectal and breast cancer treated with cetuximab or gemcitabine.
based chemotherapy. SWOG proposes to test the hypotheses that germ-line polymorphisms and expression levels of genes as well as signature profiles involved in k-ras, EGFR, angiogenesis and DNA repair will be associated with clinical outcome and toxicity in patients with metastatic pancreas cancer treated with a combination of gemcitabine with or without cetuximab in prospective randomized phase III clinical trial SWOG 0205. The specific aims of this proposal are:

- To determine whether **mutational status of k-ras** is associated with survival, progression-free survival, response, and toxicity in patients with metastatic pancreas cancer treated with gemcitabine with or without Cetuximab enrolled in a prospective randomized phase III clinical trial (SWOG 0205). gDNA will be isolated from **tumor tissue** using laser-captured microdissection from paraffin embedded tumor sections. PCR based technologies will be used to determine the specific Kras mutation.

- To determine whether **EGFR expression** measured by EGFR gene copy number, mRNA expression levels and polysomy are associated with response, time to tumor progression, survival and toxicity in patients with metastatic pancreas cancer treated with gemcitabine with or without Cetuximab enrolled in a prospective randomized phase III clinical trial (SWOG 0205). RNA will be isolated from **tumor tissue** using laser-captured microdissection from paraffin embedded tumor sections collected at time of primary diagnosis and quantitated using Taqman based technology. Gene copy number will be done by FISH.

- To determine whether **gene expression levels (RNA) in tumor tissue** in the EGFR pathway (e.g., the epithelial growth factor receptor (EGF-R, IL-8, I1-8 CXR2, VEGF, EGF, Epiregulin, Amphiregulin, IGFR) are associated with survival, progression-free survival, response and toxicity in patients with metastatic pancreas cancer treated with gemcitabine with or without Cetuximab enrolled in a prospective randomized phase III clinical trial (SWOG 0205). RNA will be isolated from **tumor tissue** using laser-captured microdissection from paraffin embedded tumor sections collected at time of primary diagnosis.

- To determine whether **germ-line polymorphisms (DNA)** of genes involved in the EGFR pathway (e.g., the epithelial growth factor receptor (EGF-R, IL-8 and its receptors, VEGF, EGF) are associated with toxicity and clinical outcome in patients with metastatic pancreas cancer treated with gemcitabine with or without Cetuximab in a prospective randomized phase III clinical trial. gDNA will be isolated from normal and tumor tissue.

**S0713: A Phase II Study of Oxaliplatin and Capecitabine in Combination with Cetuximab and Radiation in Pre-Operative Therapy of Rectal Cancer**

This randomized phase II tests whether an IGF1R antibody will increase efficacy of gemcitabine and erlotinib in advanced pancreatic cancer. Genes involved in the metabolism of gemcitabine, such as deoxycytidine kinase and deoxycytidine deaminase, DNA repair ribonucleotide reductase, and Ras mutation have been implicated by SWOG investigators in resistance to gemcitabine. Deoxycytidine kinase and deoxycytidine deaminase are two key enzymes in the activation and inactivation of deoxycytidine and its anticancer analogues. Transfection of cytidine deaminase into NIH3T3 cells demonstrated an increased resistance to ara C and gemcitabine suggesting that high expression of deoxycytidine kinase (dck) confers cellular resistance to ara-C and gemcitabine. Mutations and aberrant expression of Ras oncogenes have been implicated in the poor prognosis of human cancers and mechanisms of drug resistance. In vitro data suggest that transfection of cells with h-ras confers resistance to Ara-C, due to dck inactivity and decreased mRNA expression. The degree of Ara-C resistance correlates to the level of h-ras expression, with an inverse correlation between ras expression and deoxycytidine kinase expression. Finally, evidence that EGFR and IGF-IR have related
signaling pathways that can interact to regulate cellular proliferation, migration and invasion has stimulated interest in evaluating the combination of IGF-IR inhibition and EGFR inhibition in NSCLC. Combination EGFR and IGF-IR inhibition induced apoptosis and decreased tumor invasion, suggesting that dual blockade may overcome potential mechanisms of EGFR resistance.

The Translational Medicine Subcommittee will test k-ras test and germ-line polymorphisms and gene expression of genes involved in the EGFR and gemcitabine pathway, as an integral part of S0713. Moreover, this trial will use k-ras mutational status to determine eligibility.

**R0848: Gemcitabine, with and without Erlotinib, Followed by a Second Randomization with and without Chemoradiation, as Adjuvant Treatment for Pancreatic Head Cancer: A Phase III RTOG/SWOG/NCIC/EORTC Study**

Submission of paraffin-embedded tissue from the surgical specimen is an eligibility requirement. Primary objectives of the study are: 1) to determine the frequency and influence of epithelial mesenchymal transition (EMT) phenotype (E-cadherin, vimentin, and c-Met expression) on the outcome of patients treated with erlotinib and/or gemcitabine and 2) To determine the influence of K-Ras mutations on treatment outcome with erlotinib.

Secondary objectives include: 1) To determine the frequency of EGFR activated pathway (receptor, ligands and downstream molecule expression) and its influence on outcome in patients treated with gemcitabine and/or erlotinib, 2) To determine the association between developmental molecular markers (e.g., RON) and outcome of therapy, 3) To determine the phenotype and genotype of tumors (e.g., EMT and gemcitabine metabolizing enzymes) in patients with an early pancreas cancer recurrence after resection and adjuvant therapy.

A steering committee co-chaired by SWOG will be established to coordinate sample collection, design of laboratory studies, and data interpretation. Laboratory analyses will be performed at selected SWOG-affiliated institutions. Statistical analyses relating marker influence on the primary endpoint of survival will be done using the Cox proportional hazards model. The frequencies of various markers are not well known in adjuvant pancreatic cancer. With 770 patients we will be able to estimate the frequency of individual markers to within ± 3.6%.

**General: Developing and evaluating novel therapeutic approaches to prevent GI neoplasms in high-risk and other defined patient populations**

In collaboration with the Prevention Committee (Dr. Frank Meysken), the Gastrointestinal Committee will reinvigorate its efforts directed at conducting research on the chemoprevention of GI malignancies. This goal is a natural extension of our interest in targeted therapy, as many of the same molecular targets that are important for advanced forms of GI cancer may be relevant and potentially more effective settings for chemoprevention efforts. One such trial in late development is S0820, A Double Blind Randomized Placebo-Controlled Trial of Difluoromethylornithine (DFMO) and Sulindac to Prevent Recurrence of Adenomas in Patients with Stages I-III Colorectal Cancer. Strong epidemiologic evidence suggests regular non-steroidal anti-inflammatory drug use can prevent or even treat colonic polyps. A considerable amount of experimental literature also supports the notion that NSAIDs can prevent the development of colon cancer in multiple classical carcinogen-induction models (9, 10). Finally, previous work by SWOG investigators demonstrated DFMO is effective in reducing polyamine content in colorectal without producing side effects, at least over the duration of one year, and that resected adenoma patients treated with DFMO (500 mg) plus sulindac (150 mg) demonstrated marked reduction in adenomas overall, advanced adenomas, and multiple adenomas, as compared to placebo. (23) Additionally, the toxicity profile of that latter combination regimen was favorable. (23) S0820 will use a 2x2 factorial clinical trial design, with the primary objective being a determination whether DFMO (an irreversible inhibitor of the first enzyme, ornithine decarboxylase, in the polyamine synthesis pathway) 500 mg daily, sulindac 150 mg daily, or the combination are effective in reducing colorectal adenoma
recurrence. Secondary objectives include comparing the efficacy of combination DFMO and sulindac versus either agent alone, feasibility, and laboratory correlative studies to discover pharmacogenetic markers that improve the benefit risk ratio for S0820 adenoma risk reduction. To accomplish the latter goal, S0820 study participants will be analyzed for germ-line variants in genes related to DFMO and sulindac target action, metabolism, coagulation and auditory signal transduction.

**Contributing as both leader and active participant in Intergroup efforts**

The Southwest Oncology Group Gastrointestinal Committee is actively engaged with and fully supports the activities of the GI Intergroup. Committee (Task Force) leadership has been discussed above (GI-3). Additionally, the GI Committee has substantially enhanced collaborative efforts with other cooperative groups, in terms of jointly running potentially standard-of-care changing phase III trials (current- S0502: Phase III Trial of Imatinib Mesylate, plus or minus Bevacizumab, in Patients with Incurable Gastrointestinal Stromal Tumors; S0518: Phase III Prospective Randomized Comparison of Depot Octreotide Plus Interferon Alpha Versus Depot Octreotide Plus Bevacizumab (NSC #704865) in Advanced, Poor Prognosis Carcinoid Patients; C80405: A Phase III Trial of Irinotecan/5-FU/Leucovorin or Oxaliplatin/5-FU/Leucovorin with Bevacizumab, or Cetuximab (C225), or with the Combination of Bevacizumab and Cetuximab for Patients with Untreated Metastatic Adenocarcinoma of the Colon or Rectum; S0600: Phase III Trial of Irinotecan-Based Chemotherapy plus Cetuximab (NSC-714692) with or without Bevacizumab (NSC-704865) as Second-line Therapy for Patients with Metastatic Colorectal Cancer who have Progressed on Bevacizumab with either FOLFOX, OPTIMOX or XELOX plus Bevacizumab; future-R0848, Gemcitabine, With and Without Erlotinib, Followed by a Second Randomization with and without Chemoradiation, as Adjuvant Treatment for Pancreatic Head Cancer; A Phase III RTOG/SWOG/NCIC/EORTC Study; C80702 A Phase III Trial of FOLFOX +/- Celecoxib, Administered for 3 or 6 Months, in Patients with Fully-Resected Stage III or High-Risk Stage II Colon Cancer). Finally, the GI Committee has wholeheartedly supported projects in which it does not have a leadership stake, opening multiple studies through the CTSU mechanism and actively recruiting to same. The Gastrointestinal Cancer Committee will continue to foster open communications and work productively through the GI Intergroup during the next grant period.

**Past Critique**

Three concerns were outlined in the previous GI Committee competitive review. Response to each follows the critique:

1) Concerns about the sharing of tissue, with unclear “lines of authority”;

The reviewer concern over potential negative interactions between key institutions utilizing tissue never materialized. Specifically, cooperation between The University of Cincinnati and the University of Southern California was uniformly excellent. As an example, multiple tissues were shared from SWOG 9008, and multiple projects from that trial are still ongoing. During this grant cycle, SWOG centralized all solid tumor repositories at the University of Colorado, with strictly established rules for tissue utilization, thus eliminating any potential for non-regulated competition for tissues. Finally, the GI Committee now has a formalized Translational Medicine Subcommittee, which functions in an identical fashion as disease-site subcommittees. New ideas for using tissue are vetted early by this Subcommittee, and then brought to the general Committee for approval. All requests for tissue (beyond the protocol specified uses) must also be approved by the Southwest Oncology Group Executive Committee, as well as the GI Steering committee (for requests for 100 or more patient samples, or any request from a Phase III trial). This ensures adequate oversight and prevents any single institution from co-opting an unfair percentage of patient research materials.

2) The limited number of basic science investigators performing correlative work;

While the bulk of recent correlative work had been conducted by a single investigator (Lenz) at a single University (USC), this is no longer the case. Dr. Christopher Corless has been recruited as the co-Chair
of the Translational Medicine Subcommittee. Dr. Corless is an internationally recognized expert in genetic analyses of GI malignancies, and he has already assumed a large-scale project from a phase III trial (genotyping of GIST). Additionally, other investigators have been recruited, including Dr. Dragovich from the Arizona Cancer Center, who did the correlative work for S0127: A Phase II Study of OSI-774 (NSC #718781) in Unresectable or Metastatic Adenocarcinoma of the Stomach and Gastroesophageal Junction and who is developing a concept assessing thioredoxin-1 family protein expression in colorectal cancer, Dr. Kim from City of Hope, who will be conducting EGFR testing from S0205 specimens Additionally, lab-based personnel have been given leadership positions on disease-specific subcommittees (e.g., Dr. Lowy-Pancreatic Subcommittee), to allow their involvement in correlative projects to clinically-based protocols. The expansion to utilize MD Anderson and Fred Hutchinson investigators was discussed previously. Finally, discussion of correlative science will play a more significant role at the General GI biannual SWOG meetings, in hopes of enhancing interest and increasing participation by new members or sites.

3) A perceived limited “phase II to phase III progression” for clinical trials.

In general, few phase II trials are successful enough to proceed to phase III testing. However, during this current cycle, two recent phase III studies were based on phase II work done by SWOG investigators, including S0205: A Phase III Randomized, Open-Label Study Comparing Gemcitabine Plus Cetuximab (IMC-225) Versus Gemcitabine as First-Line Therapy of Patients with Advanced Pancreas Cancer, and S0518: Phase III Prospective Randomized Comparison of Depot Octreotide Plus Interferon Alpha Versus Depot Octreotide Plus Bevacizumab (NSC #704865) in Advanced, Poor Prognosis Carcinoid Patients. The correlative work in S0502: Phase III Trial of Imatinib Mesylate, plus or minus Bevacizumab, in Patients with Incurable Gastrointestinal Stromal Tumors is also based on basic science and clinical work conducted in phase II/III trials done directly by SWOG and by SWOG investigators. Several ongoing early phase projects have regimens with high potential for being the control arm in subsequent phase III testing, including the oxaliplatin-infusional fluorouracil schedule in S0356: Phase II Study of Oxaliplatin Plus Protracted Infusion 5-Fluorouracil and Radiation for Potentially Curable Esophageal Cancer and the cetuximab backbone in S0415: Phase II Trial of Cetuximab as second line therapy in metastatic esophageal cancer. Finally the GI Committee remains dedicated to testing novel regimens which again have strong potential for moving on, including the anti-IGFR antibody planned for testing in advanced pancreatic cancer (S0727: A Phase I and Randomized Phase II Trial of Gemcitabine + Erlotinib (NSC-71817 + IMC-A12 (NSC-742460) versus Gemcitabine + Erlotinib as First Line Treatment in Patients with Metastatic Pancreatic Cancer).
# PUBLICATIONS

## SOUTHWEST ONCOLOGY GROUP
### PUBLICATIONS LIST
#### GASTROINTESTINAL COMMITTEE

2003-2008

(includes 2002 pubs not included in previous competing renewal application)

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### COMMITTEE: GASTROINTESTINAL

#### GI MANUSCRIPTS PUBLISHED (2002)
(not reported in previous competing renewal application)

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#### GI ABSTRACTS PUBLISHED/PRESENTED (2003)

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GI MANUSCRIPTS PUBLISHED (2004)


GI ABSTRACTS PUBLISHED/PRESENTED (2004)


A phase II trial of epothilone B analogue BMS-247550 (NSC #710428) in patients with advanced pancreas cancer: a Southwest Oncology Group study.
http://meeting.ascopubs.org/cgi/content/abstract/22/14_supp/4012?maxtoshow=&HITS=10&RESULTFORMAT=&fulltext=whitehead&searchid=1&FIRSTINDEX=0&volume=22&issue=14_supp&resourcetype=HWCIT

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http://meeting.ascopubs.org/cgi/content/abstract/22/14_supp/5?maxtoshow=&HITS=10&RESULTFORMAT=&fulltext=sargent&searchid=1&FIRSTINDEX=0&volume=22&issue=14_supp&resourcetype=HWCIT

GI MANUSCRIPTS PUBLISHED (2005)


Chapter 45 – Stomach. SA Hundahl, JS Macdonald, SR Smalley. In: Chang AE, Ganz PA, Hayes DF, Gastrointestinal Committee GI- 64


9415 Phase III Southwest Oncology Group 9415/Intergroup 0153 randomized trial of fluorouracil, leucovorin, and levamisole versus fluorouracil continuous infusion and levamisole for adjuvant treatment of stage III and high-risk stage II colon cancer. EA Poplin, JK Benedetti, NC Estes, DG Haller, RJ Mayer, RM Goldberg, GR Weiss, SE Rivkin, JS Macdonald. Journal of Clinical Oncology 23(9): 1819-1825, 2005. PMID: 15774775


GI ABSTRACTS PUBLISHED/PRESENTED (2005)


GI MANUSCRIPTS PUBLISHED (2006)


S0336  Phase II trial of depsipeptide (NSC-630176) in colorectal cancer patients who have received either one or two prior chemotherapy regimens for metastatic or locally advanced, unresectable disease: a Southwest Oncology Group study. RP Whitehead, S McCoy, IS Wollner, L Wong, WG Harker, PM Hoff, PJ Gold, KG Billingsley, CD Blanke. Proc of the American Society of Clinical Oncology, *Journal of Clinical Oncology* 24(22):3542-3547, 2006. PMID: 16877719

GI ABSTRACTS PUBLISHED/PRESENTED (2006)


S0336  Phase II trial of depsipeptide (NSC-630176) in colorectal cancer patients who have received either one or two prior chemotherapy regimens for metastatic or locally advanced, unresectable disease: a Southwest Oncology Group study. RP Whitehead, S McCoy, IS Wollner, L Wong, WG Harker, PM Hoff, PJ Gold, KG Billingsley, CD Blanke. Proc of the American Society of Clinical Oncology, *Journal of Clinical Oncology* 24(22):3542-3547, 2006. PMID: 16877719
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S0336 Phase II trial of depsipeptide (NSC-630176) in colorectal cancer patients who have received either one or two prior chemotherapy regimens for metastatic or locally advanced, unresectable disease: a Southwest Oncology Group study. RP Whitehead, S McCoy, IS Wollner, L Wong, WG Harker, CD Blanke. American Society of Clinical Oncology 2006 Gastrointestinal Cancers Symposium #255, 2006.
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9008 Improved regional control and survival with “low maruyama Index” surgery in gastric cancer: autopsy findings from the Dutch D1-D2 trial. SA Hundahl, KCJM Peeters, EK Kranenbarg, H Hartgrink, CJH van de Velde. Gastric Cancer 10(2):84-86, 2007. PMID: 17577616


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R9704 Correlation of RTOG 9704 (adjuvant therapy (rx) of pancreatic adenocarcinoma (pan ca)) radiation therapy quality assurance scores (RTQA$Sc$) with survival (S). RA Abrams, KA Winter, WF Regine, H Safran, JP Hoffman, AA Konski, AB Benson, JS Macdonald, TA Rich, CG Willett.
http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/4523?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=abrams&searchid=1&FIRSTINDEX=0&volume=25&issue=18_suppl&resourcetype=HWCIT

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<td>9511</td>
<td>A Southwest Oncology Group phase II study of trimetrexate, 5FU, and leucovorin in unresectable or metastatic adenocarcinoma of the stomach.  CD Blanke, K Chansky, KL Christman, SA Hundahl, BF Issell, PJ Van Veldhuizen Jr, GT Budd, JL Abbruzzese, JS Macdonald.  Accepted by <em>American Journal of Clinical Oncology</em>, 12/3/08</td>
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<td>N9841</td>
<td>A randomized phase III non-inferiority trial of irinotecan</td>
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ABSTRACTS PUBLISHED/PRESENTED (2008)


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