Gastrointestinal Program

The NCCTG GI Committee continues to work on providing a broad menu of trials for patients with GI cancers. However, given the limited funding from NCI and focus on restricting the number of trials, the opportunities have become less. With ongoing merger of NCCTG, CALGB, and ACSOG into new group it is expected that greater opportunities may be available as we combine our resources and scientific expertise. The NCCTG GI Committee and those of the other Cooperative Groups continue to work more closely in developing and promoting joint trials, as well as setting national agendas. This activity is occurring through the GI Steering Committee. As noted previously, over the next several years there will likely be a more limited number of phase III trials in order to accrue to those trials more rapidly.

Colorectal/Anal Cancer Program:

Adjuvant Studies:

**Colon Cancer:** ECOG 5202, a trial for Stage II patients, opened in August 2005 and was endorsed by NCCTG. The trial included a randomization to FOLFOX with or without bevacizumab for the molecular high-risk population. In view of the negative data for bevacizumab in the adjuvant setting in colon cancer from NSABP C-08 and more recently, the AVANT trial, E5202 was closed to accrual in the fall of 2010. No replacement trial has been developed yet.

The NCCTG Stage III adjuvant trial (N0147) closed to accrual in November 2009 due to an interim analysis demonstrating lack of benefit from the addition of cetuximab to standard FOLFOX therapy. Efficacy data were presented at ASCO 2010 and ASCO GI 2011.

The phase III intergroup trial C80702, is underway testing in a 2x2 factorial design either 3 or 6 months of FOLFOX and either celecoxib or placebo. This trial is part of a NCCTG led international effort called IDEA (International Duration Evaluation of Adjuvant therapy) that will pool data from at least 4 ongoing international phase III clinical trials testing 3 versus 6 months of adjuvant FOLFOX/XELOX for stage III colon cancer.

**Colorectal Liver Metastases:** NCCTG has endorsed the ongoing NSABP C-11 trial which tests peri- vs postoperative FOLFOX chemotherapy for patients with resectable liver metastases. This trial initially included bevacizumab, which was dropped after the negative data of the adjuvant colon cancer trials became available.

Advanced Disease:

**First-line:** The current phase III trial for first-line therapy of metastatic colorectal cancer is jointly led by CALGB and SWOG (80405). All of the Cooperative Groups have agreed to support a single phase III trial. Patients tumor tissue is assessed for the status of KRAS. This trial randomizes patients with tumors expressing wild-type KRAS to cetuximab or bevacizumab. The physician, in consultation with the patient, will be allowed to choose either FOLFOX or FOLFIRI as chemotherapy backbone.

In coordination with other cooperative groups we are developing randomized phase II trials focusing on patients with colorectal cancer harboring KRAS mutations. Several opportunities are
being explored here with the goal to bring novel agents into first- and second-line therapy in colorectal cancer. This was the focus of a NCI-sponsored Clinical Trials Planning Meeting (CTPM) held in January 2011 with major organizational and scientific input from NCCTG leadership.

**Second-line:** SWOG and the NCCTG had jointly developed a phase III second-line trial (S0600) with the active support of NCIC. This trial was evaluating the activity of FOLFIRI (or irinotecan) and cetuximab, with or without bevacizumab, in patients with wild-type KRAS colorectal cancer who have disease progression while on either FOLFOX or XELOX and bevacizumab. Unfortunately, due to poor accrual, the trial was terminated in November 2010.

NCCTG successfully completed a phase II trial of sorafenib and bevacizumab (N054C) in the salvage therapy setting. This unique combination showed potentially promising activity in other settings and offers the potential to have a chemotherapy-free interval while maintaining disease control with a potentially less toxic combination. A phase I trial of FOLFIRI – bevacizumab plus sorafenib is underway to eventually test this combination in a randomized trial in a second-line setting in KRAS mutant colorectal cancer.

**Elderly/frail patients:** NCCTG in close collaboration with CALGB has developed a randomized phase III trial in elderly/frail patients in the first-line setting of advanced colorectal cancer to compare FOLFOX (or XELOX) + bevacizumab with fluoropyrimidine (5-FU/LV or capecitabine) plus bevacizumab (N0949). The goal of this trial is to see if this particular group of patients truly benefit from the use of oxaliplatin in their therapy. The trial was developed within strict time frame guidance of the OWEG and opened to accrual on the CTSU menu as Intergroup trial in January 2011 with the first patient on trial in February 2011. This Intergroup trial will be mirror by a similar trial in Japan led by the Japanese Clinical Oncology Group (JCOG) and a preplanned pooled analysis for overall survival together with N0949.

**Rectal Cancer:** The NCCTG-endorsed NSABP phase III trial R04 which compared infusional 5-FU vs capecitabine with or without oxaliplatin as preoperative radio-chemotherapy has finished accrual. Initial efficacy and safety data will be presented at ASCO 2011.

**Upper Gastrointestinal Cancer Program:**

**Gastroesophageal Cancer:**

**Adjuvant/Neoadjuvant:** The new neoadjuvant phase II trial (N0849) from NCCTG is now open. This trial assesses the activity of initial chemotherapy with docetaxel, oxaliplatin, and capecitabine for 2 cycles followed by a combination of chemotherapy and radiation in patients with esophageal or gastroesophageal junction adenocarcinoma. Patients are randomized to either the extended neoadjuvant therapy arm or to chemoradiation alone. Both groups gone on to surgery following the completion of the planned neoadjuvant therapy.

**Metastatic:** A randomized phase II trial of capecitabine with or without sorafenib for elderly or poor performance status patients with metastatic gastroesophageal adenocarcinoma recently closed to accrual. A new trial is in development that will assess a combination of FOLFOX with a VEGF-R2 directed inhibitor (1121B) and will open through MCCRC. While this trial will be run by Lilly through MCCRC, the trial was developed by a Mayo investigator, Dr. Harry Yoon.
Pancreatic Cancer:

Adjuvant: The GI Intergroup is discussing potential opportunities.

Locally Advanced: The trial N064A recently closed to accrual. It evaluated the potential benefit of adding an EGFR inhibitor to 5-FU and radiation using the combination of panitumumab, 5-FU, and radiation in patients with locally advanced pancreatic cancer. In addition this trial also assessed the potential benefit of maintenance therapy with panitumumab after completing radiation. Despite several attempts to develop a replacement trial, no trial has yet been approved by the GI Steering Committee.

Metastatic: Given the failure of oxaliplatin in ECOG E6201 and bevacizumab in CALGB 80303 to improve outcomes over gemcitabine alone, there remains uncertainty about where to focus current clinical research efforts. The NCCTG GI Committee recently focused on dual EGFR inhibition. N064B evaluated the combination of gemcitabine, erlotinib, and panitumumab, using a randomized phase II trial design including a contemporary comparison arm of gemcitabine and erlotinib. Discussions are still ongoing at the Pancreatic Cancer Task Force as to appropriate replacement trials. NCCTG has made several proposals that are still under discussion.

Hepatobiliary cancer:
The Phase I portion of N0745 was recently completed. This trial will assess the efficacy of bevacizumab added to sorafenib for patients with advanced disease. The randomized phase II is now open to accrual. This trial will be important to NCCTG in several ways including the potential to develop a more active regimen for HCC as well as to conduct important correlative studies.

A new trial of gemcitabine/cisplatin with either a VEGF-R2 inhibitor or PARP inhibitor (N1141) for gallbladder and biliary tract cancer is now in development. The trial is being developed jointly with SWOG. This trial should be ready for activation later this year if approved. A randomized phase II design will be used that will help to define the activity of VEGFR and PARP directed therapy in this form of cancer.

Small Bowel Cancer:
A new trial for carcinoma of the small bowel remains open. N0543 will assess the activity of a combination of capecitabine, oxaliplatin, and irinotecan utilizing UGT 1A1 testing to appropriately dose irinotecan. Accrual has been slow on this trial and members are urged to keep this trial in mind for this rare disease.

Summary of GI Program Goals

With the merger of NCCTG, CALGB, and ACOSOG in the near future in to a new cooperative group there should be greater opportunities for trials. Goals for the near future include identifying active regimens for phase II testing based on preclinical leads identified in collaboration with the Novel Therapeutics Committee. There will also be a focus of developing several new phase III trials as phase II trials show potential benefit that would justify phase III trials. The integration of translational studies whenever appropriate into trials also remains a priority.