Japanese Foundation for Multidisciplinary Treatment of Cancer JFMC 47-1202-C3 (ACHIEVE)

The ACHIEVE (Adjuvant Chemotherapy for colon cancer with High EVidence) trial, conducted by the Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC), is an open-label, randomized, phase III, multicenter study in Japan for patients with completely resected stage III colon cancer. Allocation to treatment will be centrally done with a 1:1 ratio using a randomization procedure stratified by the primary site (colon versus rectosigmoid versus multiple), the number of involved lymph nodes (1-3 versus 4 or more), regimen (FOLFOX versus XELOX), age (<70 versus ≥ 70), and participating centers. All participating centers will access the randomization system through a Web-based program. The trial treatments will consist of 3 or 6 months of chemotherapy with modified FOLFOX6 (6 or 12 cycles) or XELOX (4 or 8 cycles).

The primary study objective is to compare whether a 3-month treatment is at least not inferior to a 6-month treatment (modified FOLFOX6 [6 cycles versus 12 cycles] or XELOX [4 cycles versus 8 cycles]) in terms of relapse-free survival (RFS), which refers to recurrence of colon cancer or death from any cause in patients with stage III radically resected colon cancer. No statistical efficacy analyses for the primary study objective are planned for the JFMC participation in IDEA; the objective is to accrue up to 1,200 patients toward the overall IDEA goal.

The secondary study objectives include:

- Disease-free survival (DFS)
- Time to treatment failure (TTF)
- Overall survival (OS)
- Toxicity (according to the NCI-CTAE v 4.0)
- Completion rate of the study treatment
- Percent of dose received versus planned dose
- The correlation of the clinical outcome with the number of involved lymph nodes and that of the dissected lymph nodes
- Incidence and nature of peripheral sensory neuropathy (PSN)

The trial will also identify single nucleotide polymorphisms (SNPs) using the genome-wide association study (GWAS) associated with toxicity and clinical outcome.

This trial will open in August 2012 in 300 centers. Once all centers have activated the trial, the target monthly accrual is 50 patients and total planned accrual is 1,200 patients.

Masaki Mori, M.D., Ph.D., at the Osaka University, Graduate School of Medicine, Department of Gastroenterological Surgery; Atsushi Ohtsu, M.D., Ph.D., at the National Cancer Center Hospital East, Research Center for Innovative Oncology; and Takayuki Yoshino, M.D., at the National Cancer Center Hospital East, Department of Gastroenterology and Gastrointestinal Oncology, are the study co-principal investigators for this trial.
Accrual Update

**PRODIGE-Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR) trial**
Activation date: May 2, 2009  
Current status: Active, recruitment ongoing  
Planned accrual: 2,000 patients  
Sites open: 135 open centers; 122 centers have enrolled at least 1 patient  
Current accrual: 1,136 patients randomized (all stage III)  
Other activity: Amendment for stage II high-risk patients is completed and inclusion for these patients will open soon.

**Short Course Oncology Treatment (SCOT) trial**
Activation date: March 27, 2008  
Current status: Open in the United Kingdom and Australia  
Planned accrual: 9,500 patients  
Sites open: 159 centers open in United Kingdom, 31 in Australia, 7 in Denmark, 19 in Spain  
Current accrual: 3,656 patients randomized; current accrual rate is 142 patients per month (approximately 70% of these patients have stage III colon cancer)  
Other activity: Other centers from Germany, Switzerland and Sweden are interested in participating in SCOT.

**Cancer and Leukemia Group B (CALGB)/Southwest Oncology Group (SWOG) trial C80702**
Activation date: July 2010  
Current status: Open  
Planned accrual: 2,500 patients  
Sites open: 588 sites are listed in ClinicalTrials.gov — endorsed by all adult oncology treatment cooperative groups in the United States and Canada  
Current accrual: 590 patients; current accrual rate is 40 patients per month.

**Three or Six Colon Adjuvant (TOSCA) trial**
Activation date: First patient enrolled on June 20, 2007  
Current status: Open  
Planned accrual: 3,500 patients  
Sites open: 130 sites  
Current accrual: 3,249 patients (2,113 patients with stage III colon cancer); current accrual rate is 59 patients per month.

**HORG trial**
Activation date: October 2010  
Current status: Open  
Planned accrual: 1,000 patients  
Sites open: 15 sites have been activated (13 have at least 1 patient enrolled)  
Current accrual: 470 patients (169 patients with high-risk stage II disease, the remaining 301 patients with stage III disease); accrual rate is 16 patients per month for last 3 months.

**Japanese Foundation for Multidisciplinary Treatment of Cancer JFMC 47-1202-C3 (ACHIEVE) trial**
Activation date: To open August 2012  
Planned accrual: 1,200 patients  
Sites open: Trial will be open at 300 centers; once all centers have activated the trial; the target accrual is 50 patients per month.
IDEA Overview

The purpose of International Duration Evaluation of Adjuvant Chemotherapy (IDEA) is to facilitate the collaboration among multiple individual trials conducted around the world for a single, pooled analysis of the primary aim: To test whether 3 months of oxaliplatin-based adjuvant therapy is non-inferior for disease-free survival (DFS) to 6 months of the identical therapy in patients with stage III colon cancer.

The IDEA Steering Committee is comprised of 2 members from each group coordinating an individual trial, plus 2 members from a Secretariat, North Central Cancer Treatment Group (NCCTG), who are responsible for coordinating the data pooling and the joint analysis. (See list on page 1.) Members of IDEA have agreed to pool the data from their individual trials to allow a definitive analysis consisting of at least 10,500 patients, using DFS as the primary endpoint. Non-inferiority will be declared if the 2-sided 95% confidence interval for the hazard ratio comparing 3 to 6 months of therapy lies entirely below 1.10. A sample size of 10,500 patients provides 90% power, based on an expected accrual duration of 3.5 years, 3 years minimum follow-up, and an expected 3-year DFS rate in the control group of 72% to declare non-inferiority if the true hazard ratio is 1.0.

Individual trials included in IDEA may address additional trial-specific hypotheses in a factorial design; the analyses of these additional hypotheses will be trial specific and not involve IDEA. The IDEA pooled analysis will consist only of stage III colon cancer patients enrolled in these trials. Only patients randomized to 3 or 6 months of a FOLFOX regimen (FOLFOX4 or mFOLFOX6) or XELOX will be included in the pooled analysis. The trials in IDEA share accrual information on an ongoing basis (at least every 6 months). The final pooled analysis will be conducted jointly by the IDEA Steering Committee, with the Secretariat and main data analysis site at Mayo Clinic/NCCTG. Currently, 5 trials in IDEA are actively enrolling patients.

Contact information

For further information on IDEA, contact the NCCTG Secretariat at:
NCCTG Operations Office
200 First Street S.W.
Rochester, Minnesota 55905
E-mail: IDEA@mayo.edu

News/Updates

New drugs show improved survival rates for patients with colorectal cancer

ASCO 2012 saw the presentation of the long-awaited results of the ML18147 phase III trial, which tested the efficacy of bevacizumab beyond progression (BBP) added to chemotherapy in metastatic colorectal cancer (mCRC). This trial was initiated by the German AIO and picked up by Roche when intriguing results from the BRiTE observational study suggested that BBP improved overall survival in mCRC.

A total of 820 patients who had received first-line palliative therapy with a bevacizumab-based combination were randomized at progression to either continue bevacizumab with another dealer’s choice chemotherapy backbone or stop bevacizumab. The primary endpoint of the study, improvement in overall survival, was reached with a hazard ratio (HR) of 0.81 (95% CI: 0.69-0.94) and a median improvement of 1.4 months (11.2 versus 9.8 months, p=0.0062). This effect was confirmed in all evaluated subgroups and supported by the results of progression-free survival, which demonstrated superiority for the BBP arm (HR 0.68, median 5.7 versus 4.1 months, p<0.0001). In addition, no increase in response rate was seen in the BBP group and the response rates seen in both arms in second-line therapy were low, with around 4% to 5%. No new or unexpected safety issues emerged.

The trial is noteworthy for several reasons. It confirms the efficacy of a clinical practice widely used in the United States and other countries, even if the overall benefit does not reach the magnitude suggested by the BRiTE study. It also confirms the clinical usefulness of prolonged VEGF inhibition, which was already suggested by the results of the VELOUR study. In addition, it challenges the “black-or-white” notion of tumor resistance to medical therapy and thereby opens the door for new treatment strategies and trial designs in mCRC.