Collaboration Update

IDEA crosses original 10,500 patient enrollment goal

The combined patient accrual for the trials of the IDEA Collaboration has just passed the original enrollment goal of 10,500 patients with stage III colon cancer. Hearty congratulations to all of those involved in each of the 6 IDEA trials and, most importantly, our sincere thank you to all patients who have participated in this first-of-its-kind international collaboration. Two trials have now closed to accrual (SCOT and TOSCA) but 4 trials remain open, and further accrual remains critical. Every patient enrolled will allow us to answer this critical question of comparing the effectiveness of 3 versus 6 months of adjuvant therapy more quickly, as well as adding to the definitive nature of the analysis. If each trial enrolls to its full capacity, the total IDEA accrual will exceed 12,500 patients.

The IDEA Steering Committee met at the European Cancer Congress 2013 in Amsterdam in October. At that meeting, the progress of each trial was reviewed, including accrual, patient baseline characteristics, and dosing information. A critical issue for the integrity of the IDEA question is the cumulative dose delivered of oxaliplatin on the 6-month arm. The committee reviewed this issue in detail. All 6 trials are reporting median cumulative dosing of oxaliplatin ranging from 700 mg/m2 to 780 mg/m2, which is very consistent with the data from the original trial of FOLFOX4 in the adjuvant setting (the MOSAIC trial, Andre, *New England Journal of Medicine* 2004). The Steering Committee will continue to review this data at its regular meetings.

In addition, the Steering Committee reviewed the timing of the preplanned interim analysis. The analysis is scheduled to occur after 50% of the 3390 required disease-free survival (DFS) events have been observed. Based on the current number of events, this interim analysis will likely occur in 2014. The Steering Committee is now monitoring the number of DFS events on a quarterly basis to define the timing of the interim analysis more closely.

Congratulations and thanks to all IDEA trial investigators, study staff, and patients for their commitment to the IDEA project.

IDEA Steering Committee: Timothy Iveson, M.D., principal investigator (PI), Short Course Oncology Treatment (SCOT) trial; Jim Paul, M.S., SCOT trial; Roberto Labianca, M.D., co-PI, Three or Six Colon Adjuvant (TOSCA) trial; Alberto Sobrero, M.D., co-PI, TOSCA trial; Jeffrey Meyerhardt, M.D., M.P.H., Cancer and Leukemia Group B (CALGB) chair, C80702 trial; Anthony Shields, M.D., Ph.D., PI, Southwest Oncology Group (SWOG), C80702 trial; Thierry André, M.D., co-PI, PRODIGE-Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR) trial; Julien Taieb, M.D., co-PI, PRODIGE-GERCOR trial; Atsushi Ohtsu, M.D., co-PI, ACHIEVE trial; Takayuki Yoshino, M.D., co-PI, ACHIEVE trial; Ioannis Souglakos, M.D., PI, Hellenic Oncology Research Group (HORG); Axel Grothey, M.D., North Central Cancer Treatment Group (NCCTG) Secretariat; Daniel Sargent, Ph.D., NCCTG Secretariat.

IDEA Coordination Committee: Donna Niedzwiecki, Ph.D., (CALGB); Irene Floriani, Ph.D., (TOSCA); Jim Paul, M.S., (SCOT); Frank Bonnetain, Ph.D., (PRODIGE-GERCOR); and Daniel Sargent, Ph.D., (Secretariat).
Accrual Update

**PRODIGE-Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR) trial**

**Activation date:** May 2, 2009  
**Current status:** Active, recruitment ongoing  
**Planned accrual:** 2000 patients  
**Sites open:** 136 open centers, 122 centers enrolled at least 1 patient  
**Current accrual:** 1743 patients randomized (all patients with stage III colon cancer); 1576 patients on FOLFOX (90%), 167 patients on XELOX (10%); current accrual rate is approximately 35 patients per month

**Short Course Oncology Treatment (SCOT) trial**

**Activation date:** March 27, 2008  
**Current status:** Closing in November 2013  
**Planned accrual:** 9500  
**Sites open:** 163 centers open in United Kingdom, 32 in Australia, 10 in Denmark, 19 in Spain, 14 in Sweden, and 5 in New Zealand  
**Current accrual:** 5836 patients randomized (approximately 67% of patients with stage III colon cancer); current accrual rate is 110 patients per month; study to close in November 2013 with an estimated total of 6000 patients.  
**Other activity:** Translational sample collection of tumor tissue and blood under way

**Cancer and Leukemia Group B (CALGB)/Southwest Oncology Group (SWOG) trial C80702**

**Activation date:** July 2010  
**Current status:** Open  
**Planned accrual:** 2500 patients  
**Sites open:** 588 sites are listed in ClinicalTrials.gov —endorsed by all adult oncology treatment cooperative groups in the US and Canada  
**Current accrual:** 1364 patients; current accrual rate is approximately 45-50 patients per month

**Three or Six Colon Adjuvant (TOSCA) trial**

**Activation date:** First patient enrolled on June 20, 2007  
**Current status:** Closed  
**Planned accrual:** 3750  
**Sites open:** 128 sites  
**Current accrual:** 3759 patients (2436 patients with stage III colon cancer and 1323 patients with high-risk stage II colon cancer)

**HORG trial**

**Activation date:** October 2010  
**Current status:** Open  
**Planned accrual:** 1000 patients  
**Sites open:** 15 sites have been activated (13 have at least one patient enrolled)  
**Current accrual:** 745 patients (227 patients with high-risk stage II colon cancer and the remaining 518 patients with stage III disease); accrual rate is 19 patients per month for last 3 months

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

**Activation date:** August 1, 2012  
**Current status:** Open  
**Planned accrual:** 1200 patients  
**Sites open:** 294 sites open; target is 453 sites; once all centers have activated the trial, the target accrual is 50 patients per month  
**Current Accrual:** 731 patients (all patients with stage III colon cancer)
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. 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 1.12. 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, 4 trials in IDEA are actively enrolling patients.

News/Updates

One of the hot topics that has recently emerged in the adjuvant therapy of colon cancers is the question of whether aspirin can be regarded as a highly effective targeted agent for patients with PIK3CA mutated cancers. This issue was raised last year in a very provocative paper in the New England Journal of Medicine by Liao et al in 2012. In this retrospective analysis of large cohort studies, researchers found that aspirin demonstrated a highly statistically significant decrease in the risk of cancer recurrence and cancer-related death in patients with PIK3CA mutated colorectal cancers.

This observation has been confirmed by an analysis of the UK Vioxx in Colorectal Cancer Therapy: Definition of Optimal Regime (VICTOR) trial results. In this trial, researchers tried to investigate the role of adjuvant rofecoxib after resection of colon and rectal cancers. Due to the cardiovascular side effects of rofecoxib, which emerged while the trial was conducted, the actual study question could not be answered, not least since the median duration of rofecoxib therapy was less than 8 months. However, the VICTOR trial allowed patients on low-dose aspirin (<100 mg/day) to be enrolled, and the results for these patients formed the basis for the current analysis published in the Journal of Clinical Oncology by Domingo et al. Again, patients with PIK3CA mutated colorectal cancers who were on low-dose aspirin enjoyed a remarkable benefit in terms of decreased tumor recurrence and cancer-specific mortality. No benefit was observed for cancers not harboring PIK3CA mutations, and the effect appeared to be independent of COX-2 expression levels.

The key questions, which are currently being considered by an international consortium of investigators, are whether the data needs to be confirmed in a prospective randomized trial, and if such a trial is feasible/ethical for patients with documented PIK3CA mutated colorectal cancers.