

SPOTLIGHT ON TRIALS

Alliance Rectal Cancer Trial May Influence Future Treatment

NCCTG N1048 (PROSPECT) A phase II/III trial of neoadjuvant FOLFOX, with selective use of combined modality chemoradiation versus preoperative combined modality chemoradiation for locally advanced rectal cancer patients undergoing low anterior resection with total mesorectal excision

Approximately 40,000 new cases of rectal cancer are diagnosed each year in the United States, according to the American Cancer Society. About 22,000 deaths annually are expected. Currently, the standard of care for locally advanced rectal cancer is trimodality therapy using chemotherapy and pelvic radiation (or 5FUCMT) prior to surgery. Although radiation therapy to the pelvis has been a standard and important part of the treatment for rectal cancer and has been shown to decrease cancer recurrence in the same area in the pelvis, some patients experience undesirable side effects from the radiation. It is not yet known whether some patients can avoid radiation therapy if their rectal cancer responds to neoadjuvant chemotherapy (FOLFOX). In this study, Alliance investigators will learn whether radiation can be safely omitted for some patients.

NCCTG N1048, also referred to as PROSPECT (Preoperative radiation or selective preoperative radiation and evaluation before chemotherapy and TME) is a randomized phase II/III trial of the selective use of radiation therapy in intermediate risk rectal cancer.

Alliance investigators will study how well chemotherapy with selective use of radiation compares to consistent use of radiation therapy in treating rectal cancer patients. All patients will undergo surgery. Investigators hypothesize that if patients respond to neoadjuvant chemotherapy (FOLFOX), it will be safe to omit the 5FUCMT without compromising outcomes. It is anticipated that this strategy will minimize toxicity and enhance outcomes for select locally advanced rectal cancer patients. The study is not designed to eliminate radiation, but rather to see if it can be used selectively as opposed to consistently for all patients.

Patients will be randomized to either neoadjuvant combined modality therapy with 5FUCMT or to initial pre-operative chemotherapy with selective use of radiation depending on response to neoadjuvant chemotherapy (FOLFOX). The phase II/III design is efficient and includes the phase III comparison. The phase III component will evaluate clinical outcomes of both groups relative to co-primary endpoints of disease-free survival and time to local recurrence (TLR). The phase II component will focus on safety and early evidence of inferiority of the intervention group compared to the other group based on the pelvic R0 resection rate and TLR.

General eligibility criteria include patients who are at least 18 years old, have clinical stage II or III rectal cancer located 5-12 cm from the anal verge; and have had no prior cancer treatment. Refer to the NCCTG N0148 (PROSPECT) protocol document, which can be found on the Cancer Trials Support Unit (CTSUSU) menu at www.ctsu.org, for complete information on the trial design, treatment plan and patient eligibility.

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This study has the potential to personalize rectal cancer therapy and increase the number of available approaches to treatment. It also includes clinical (quality of life and PRO-CTCAE) and biological (genomic characterizations, immunologic studies, and pharmacogenomics) correlative studies.

NCCTG N0148 is currently available on the CTSU menu (www.ctsu.org) to all Alliance members and most other cooperative groups.

The study chairs are Deborah Schrag, MD, Dana Farber Cancer Institute, e-mail: deb_schrag@dfci.harvard.edu; Robert McWilliams, MD, Mayo Clinic, e-mail: mcwilliams.robert@mayo.edu; and Alessandro Fichera, MD, University of Chicago, e-mail: afichera@surgery.bsd.uchicago.edu.

Alliance and NCI Collaborate to Evaluate Rare Cancers

Alliance A091103 Phase II study of the angiopoietin-1 and -2 peptibody AMG 386 for the treatment of angiosarcoma

Angiosarcomas (AS) are rare, aggressive tumors that account for only one to two percent of soft tissue sarcomas. The incidence of AS is equally distributed between men and women but tends to occur more commonly in older patients.¹⁻³ It can occur in any soft tissue structure or the viscera; cutaneous lesions are found in the head and neck region, typically the scalp.⁴ The overall five-year survival is 35 percent.^{1-2,5}

The most optimistic surgical series of 82 patients with localized disease demonstrated a median survival of seven months with only 60 percent of patients alive for more than five years.⁶ Surgical resection remains the only potentially curative approach for this disease; however, both local and distant recurrences are quite common.² Chemotherapy is typically reserved for unresectable disease although there is limited published data to guide chemotherapy treatment decisions because there are few prospective, randomized clinical trials.

Anti-angiogenic therapies that inhibit the growth of new blood vessels have been explored for this disease with interest since single agent bevacizumab has been reported to produce a response rate of 12 percent.⁷

AMG 386 is a novel, intravenously administered peptide-Fc fusion protein that binds to and sequesters angiopoietin 1 and 2, preventing their interaction with TIE2 and inhibiting tumor endothelial cell growth. Angiosarcomas are known to have high expression of angiopoietin 2 and up-regulation of TIE2. Patients receiving AMG 386 have reported experiencing edema, a unique adverse effect thought to be related to the drug's activity on the lymphatic system. Other possible effects include ascites, pleural effusion, and infusion reactions.

In Alliance A091103, the Alliance for Clinical Trials in Oncology has collaborated with the National Cancer Institute's N01 Program to advance phase II studies and pilot protocols that explore promising combination therapies and high priority studies that are pivotal for drug development. This trial, which examines a rare solid tumor, will rapidly evaluate the biologic effects of an NCI-sponsored anticancer agent on molecular targets and determine clinically relevant outcomes.

Alliance A091103 is a straightforward single-arm phase II trial that is enrolling patients with measurable disease; up to four prior systemic treatment regimens are allowed. The trial aims to determine the overall response rate defined as complete response plus partial response, in patients with advanced, unresectable angiosarcoma treated with AMG 386. It also aims to evaluate the progression free survival and overall survival of patients with advanced, unresectable angiosarcoma treated with AMG 386.

Alliance A091103 is currently available on the CTSU menu (www.ctsu.org) to all Alliance members. Refer to the protocols for complete information about the trial design and patient eligibility. Note that at Memorial Sloan-Kettering Cancer Center only, optional pre- and post-cycle 1 biopsies will be obtained to explore correlation of baseline expression and changes in expression of angiopoietin 2 and TIE2 in tumor with benefit from therapy.

The Study Chair is Sandra P. D'Angelo, MD, Memorial Sloan-Kettering Cancer Center, e-mail: dangelos@mskcc.org.

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2. Mark, R.J., et al., Angiosarcoma. A report of 67 patients and a review of the literature. *Cancer*, 1996. 77(11): p. 2400-6.
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4. Young, R.J., et al., Angiosarcoma. *Lancet Oncol*, 2010. 11(10): p. 983-91.
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7. Agulnik M, O.S., Von Mehren M, et al. An open-label multicenter phase II study of bevacizumab for the treatment of angiosarcoma. *Proc Am Soc Clin Oncol*, 2009. 27.

Large-scale Alliance Brain Tumor Study Opens for Enrollment

Alliance A071101 A phase II randomized trial comparing the efficacy of heat shock protein-peptide complex-96 (HSPPC-96) (NSC #725085, Alliance IND# 15380) vaccine given with bevacizumab versus bevacizumab alone in the treatment of surgically resectable recurrent glioblastoma multiforme (GBM)

The Alliance for Clinical Trials in Oncology has recently opened a large-scale phase II randomized trial comparing the efficacy of HSPPC-96 given with bevacizumab versus bevacizumab alone in the treatment of surgically resectable recurrent glioblastoma multiforme (GBM). Alliance researchers plan to enroll approximately 222 patients across Alliance sites to evaluate overall survival, progression free survival and safety.

Alliance A071101 represents the largest vaccine study in brain tumors ever undertaken by the Alliance as well as the National Cancer Institute (NCI). The NCI will provide the Alliance for Clinical Trials in Oncology Foundation an additional \$3,000 per patient, an increase over the \$2,000 payment due to the complex nature of the trial. The Foundation will provide additional funds to sites as outlined in the funding sheet posted on the CTSU website (www.ctsu.org).

Background. Primary malignant brain tumors are uniformly fatal, and the five-year survival rate for the highest grade of malignant glial neoplasm, GBM, is now less than four percent.¹ Improvements in conventional treatment modalities have provided some progress; however, median survival remains at just over one year from initial diagnosis for patients treated at tertiary care centers.² Currently approved therapy for a newly diagnosed GBM patient in the United States includes maximal surgical resection followed by radiation and temozolomide.¹ Upon recurrence there are few approved options and these include surgical implantation of chemotherapy bearing wafers (polifeprosan 20 with carmustine implant, Gliadel® Wafer) and systemic administration of the anti-angiogenic agent bevacizumab, which has shown a partial response rate of 20 percent in one trial, and 26 percent in another.³⁻⁵ Each of these therapies has shown modest improvement in survival of patients with recurrent GBM, with notable treatment related toxicities including wound breakdown after surgical resection.⁶

Alliance A071101 is an important trial because there are currently no approved adjuvant treatments in recurrent GBM that significantly extend survival. This trial is designed to provide sound evidence towards determining whether an autologous active immunotherapy, HSPPC-96, used as an adjuvant treatment to surgery and in combination (either concomitantly post-surgery or serially at the point of progression) with the best available and approved therapy, bevacizumab, in recurrent GBM can extend overall survival. Since this trial includes an arm of bevacizumab alone, this also helps to better characterize the effect of bevacizumab on overall survival in a randomized, controlled setting, which remains an important open clinical question. Beyond the primary goal of demonstrating an impact on overall survival, this trial will also advance the biological understanding of a vital area of cancer research. The use of cancer vaccines in combination with other immune-based, targeted agents has been an area of increasing focus but clinical efforts to undertake combination trials have been limited to date. Alliance A071101 provides the opportunity to advance the understanding of cancer vaccines and combination therapy in a meaningful clinical setting. In addition, positive findings in recurrent GBM would likely have implications for utility of HSPPC-96 in surgically resectable newly diagnosed GBM. From a biological perspective, positive findings could also open additional avenues of research with HSPPC-96 and bevacizumab in other cancer indications.

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Alliance Selects PI of New NCI Community Oncology Research Program



Buckner

The Alliance for Clinical Trials in Oncology Board of Directors recently approved the selection of **Jan C. Buckner, MD**, of Mayo Clinic, to serve as the Director of the Alliance Cancer Control Program (CCP) and the Principal Investigator of the Alliance National Cancer Institute Community Oncology Research Program (NCI NCORP) grant application. Dr. Buckner will be the principal investigator for the funding application that the Alliance will prepare later this year, and submit to the NCI, to replace the current U10 CCOP Research Base funding awards held by the Alliance's three legacy groups American College of Surgeons Oncology Group (ACOSOG), Cancer and Leukemia Group B (CALGB), and North Central Cancer Treatment Group (NCCTG).

NCORP is a recently developed NCI program derived in part from the realignment of the Community Clinical Oncology Program (CCOP), Minority-Based CCOP (MBCCOP), and NCI Community Cancer Centers Program (NCCCP). It aims to build on the strengths of these now combined programs, building a community-based network to support a wide range of clinical, cancer disparities, and cancer care delivery research.

Dr. Buckner, Professor of Oncology at Mayo Medical School, has led a distinguished career in academics, research, clinical treatment and administration. As a neuro-oncologist, he specializes in the research and treatment of cancers affecting the brain and nervous system. Dr. Buckner has authored or co-authored nearly 200 articles and has given more than 70 scientific lectures and presentations. He is a past recipient of the Society for Neuro-Oncology Award for Excellence in Clinical Research (2001). Currently within the Alliance, Dr. Buckner serves as the Principal Investigator and Director of CCP, and is an active member of the Board of Directors, the Program Operations Committee as well as several other committees.

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Alliance A071101 is currently available on the CTSU menu (ctsu.org) to all Alliance members. Refer to the protocols for complete information about the trial design and patient eligibility..

The study chair is Andrew T. Parsa MD, PhD, University of California, San Francisco, e-mail: parsaa@neurosurg.ucsf.edu.

Sources

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Four Statisticians Receive Grants to Support Alliance Statistical Research Projects

As part of a new program, the Alliance Statistics and Data Center has recently allocated and awarded grants to promote biostatistics research by Alliance PhD statisticians. Four faculty statisticians have received two grants totaling \$30,000 for up to 12 months to either generate a first-author manuscript(s) or secure dedicated time for an extramural grant application as a PI. The small grants program has been established to primarily fund protected time for a PhD statistician to perform or develop statistical methodological research; however a small portion of the funds can be used for support staff (MS/SPA) to help with data set up, run simulations, generate figures, etc. All proposed research is directly relevant to the Alliance.

Proposals and award recipients include “*Statistical Analysis of Overall Survival in Complex Situations of Phase III Clinical Trials*,” by **Rui Qin, PhD**, Assistant Professor of Biostatistics at Mayo Clinic, and **Susan Halabi, PhD**, Professor of Biostatistics and Bioinformatics at Duke University School of Medicine, and “*Adaptive Phase II Clinical Trial to Evaluate Novel Therapy Across Multiple Biomarker-based Subgroups in the Presence of Multiple Disease Endpoints: Design, Evaluation, and Implementation in Alliance Studies*,” by **Lindsay A. Renfro, PhD**, Division of Biomedical Statistics and Informatics at Mayo Clinic, and **Donald A. Berry, PhD**, Professor in the Department of Biostatistics at the University of Texas MD Anderson Cancer Center.

2013 Alliance Meeting Abstract Submissions

The deadlines for submission of Alliance abstracts to the **American Society for Hematology (ASH)** meeting are quickly approaching:

- **July 25:** deadline to submit to the Alliance: Publications@AllianceNCTN.org
- **August 8:** deadline to submit to ASH meeting
- **December 7-10:** ASH meeting

All draft abstracts from Alliance for Clinical Trials in Oncology (including all three legacy groups: ACOSOG, CALGB and NCTG) must be submitted by the date indicated above to the Alliance by e-mail to Publications@AllianceNCTN.org. This deadline is firm, and is required to ensure time for central review of content, as well as review of author lists. Adherence to this guideline will assure sufficient time for the each lead investigator to submit to ASH.

All Alliance abstracts must follow this process. Independent submission of work related to the Alliance without this proper review is not permitted.

Abstract Requirements

An Alliance abstract should contain the following information:
Study numbers

- For an Alliance study X, the study number should appear in the title as “Alliance X”

- For a legacy study, the study number should appear in the title as “[Legacy Group Name] X (Alliance)” (e.g., “CALGB 40101 (Alliance)”)
- If multiple studies are involved and the title cannot accommodate all of the numbers, the study numbers must appear in the text of the abstract.

Authors

- The Alliance statistician must appear in the list of authors, usually as second author
- The list of authors should reflect study participation, including patient accrual and scientific input

Affiliation and grant support

- Provide institutional affiliation for each author

Corresponding author

- Provide the name and contact information of the corresponding author

Accepted Abstracts

Send the publications coordinator the acceptance notification and final accepted abstract within one week after hearing from meeting or association.

Questions: If you have questions about the abstract review process, contact the publications coordinator at Publications@AllianceNCTN.org.



Web Corner: Navigating the Alliance Website

Helpful Tips for Accessing Information Online

HOW THE ALLIANCE SITE IS MANAGED & WHO TO CONTACT

Web Operations Manager

This individual is responsible for the day-to-day function and operation of all Alliance web presences, including the website and wikis (team or committee-specific websites).

Alliance Website Team

This team comprises members from all functional units within the Alliance plus IS staff, Web Operations Manager and Web Content Administrators, and is responsible for web development and management. This team reports to the Alliance Program Operations Committee.

Website Content

All requests for website revisions or additions should be submitted to the Web Operations Manager by e-mail at info@allianceNCTN.org.

- Minor requests (such as bugs, broken links and information updates) are handled directly by the Web Operations Manager.
- Requests for new menu items or new pages are sent to the Alliance Program Operations Committee for review and approval.

Website Feedback

For all questions, suggestions or concerns about the website, send an e-mail to info@allianceNCTN.org.

Call for Posters: Upcoming Alliance Group Meeting

The Alliance will sponsor a poster session at the Group meeting held November 7-9, 2013. If you presented at a meeting between November 2012 and November 2013, please contact Mary Cate Zipprich (mzipprich@partners.org) to express your interest in participating in the poster session and to obtain more details.

Future Meeting Dates

2013 Group Meeting

November 7-9, 2013
Open to Alliance members

2014 Committee Meetings

May 8-10, 2014
Open to Alliance committee members only

Group Meeting

November 6-8, 2014
Open to Alliance members

All meetings will be held at the **InterContinental Chicago O'Hare**
5300 N. River Road, Rosemont, IL

For meeting and travel inquiries, contact Katherine Faherty
e-mail: kefaherty@partners.org
phone: 617-525-3022

After June 21, contact Holly DeSimone
e-mail: hdesimone@partners.org
phone: 617-732-8919

For more information on the Alliance and updates about meetings, visit AllianceforClinicalTrialsinOncology.org

Did You Know ...

The new **Alliance Service Center** is now open! It offers **triage support** for Alliance information systems, along with user authorization, access, connectivity and password resets. Hours are **8 am to 5:30 pm ET** Monday through Friday, excluding holidays. For general information, **call** 877-442-2542 or **e-mail** AllianceServiceCenter@allianceNCTN.org.

Photos!

New Alliance Website

Want to see your institution featured prominently on the new Alliance website? If so, send us your photos. We welcome photos of all Alliance members and institutions. Just send them to us with a confirmation that all individuals pictured have given their consent for web posting to *Alliance News* at jowens@uchicago.edu. Also, make sure to include a caption with the date, location, and names of individuals in the photos.