Alliance for Clinical Trials in Oncology
NEWS
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info@alliance-website.org

SPOTLIGHT ON TRIALS

Three Alliance Studies Target High-risk Patient Populations

According to *Cancer Facts & Figures 2012*, published by the American Cancer Society, lung, bladder and kidney cancer are among the most commonly diagnosed cancers in the United States. Lung cancer has an incidence of more than 226,000 new cases annually, and about 160,000 deaths each year. Bladder and kidney cancer have about 73,000 and 64,000 new cases respectively, and about 14,800 and 13,500 deaths each year. Many new advances in cancer treatment and supportive care have prolonged survival for many patients with these cancers; however, disease recurrence is very common and sometimes occurs rapidly after disease remission. In three ongoing trials, Alliance researchers are evaluating new treatment approaches for patients with these high-risk malignancies.

Study Details
ACOSOG Z4099/RTOG 1021

- Study PI: Hiran Fernando, MD
- Target enrollment of 420 patients
- Primary study endpoint: three-year overall survival (OS); secondary endpoints: loco-regional recurrence-free survival, disease-free survival, pulmonary function, and adverse events
- Endorsed by RTOG, and open for accrual through the CTSU

ACOSOG Z4099/RTOG 1021 A Randomized Phase III Study of Sublobar Resection (+/- Brachytherapy) versus Stereotactic Body Radiation Therapy in High Risk Patients with Stage I Non-Small Cell Lung Cancer (NSCLC)

This study represents significant collaboration between radiation oncologists and thoracic surgeons to provide two different local therapies for lung cancer. Currently, sublobar resection (wedge or segmentectomy) is the standard of care for high-risk patients who cannot tolerate lobectomy but have "operable" disease. Stereotactic body radiation therapy (SBRT) – a technique that delivers high doses of radiation precisely to tumors in the body – is rapidly becoming the new standard of care for patients with high-risk, operable disease. The ability to deliver radiation to a localized three-dimensional area allows the delivery of higher doses than previously possible, while preserving lung function. SBRT has resulted in excellent local control of cancer, with minimal morbidity. This has led to interest in using SBRT in the treatment of patients with high-risk operable disease where the benefits of a lower risk therapy may offer advantages over surgery for this patient group which often has co-morbidities. Aside from procedural risks, there are several other factors to consider when weighing the benefits of sublobar resection versus SBRT. With sublobar resection, the tumor histology and success of resection will be known. Lymph node dissection or sampling

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can be undertaken, sometimes resulting in the identification of other occult disease. Therefore, better pathological staging can inform the decision of an adjuvant regimen and may result in better loco-regional control and potentially an increase in survival. On the other hand, in high-risk patients, better loco-regional control may not translate into better survival, and treatment with SBRT may result in better quality of life for patients due to a decrease in treatment-related complications.

The primary endpoint of Z4099/RTOG 1021 is to demonstrate that three-year survival will not be inferior with SBRT compared to surgery with brachytherapy. Other endpoints such as early and late morbidity, quality of life, impact of treatment on pulmonary function and patterns of recurrence will be measured using standardized definitions.

There are several challenges to accrual for this type of study. The primary one is the ability to explain the different treatment approaches to patients and why they should consider randomization between the two. However, many investigators, are comfortable with the study design as evidenced by the growing number of activated sites and consider this an important clinical question to answer. The results of Z4099/RTOG 1021 have the potential to significantly change the standard of care, and also determine which patients are the best candidates for each treatment approach.

The study protocol for ACOSOG Z4099/RTOG 1021 can be found on the CTSU website (www.ctsu.org) with complete information on the trial design, patient eligibility and the treatment plan.

The Study Chair is Hiran Fernando, MD, of Boston Medical Center, e-mail: hiran.fernando@bmc.org. The Study Co-Chair is Robert Timmerman, MD, of Southwestern Medical Center, e-mail: robert.timmerman@utsouthwestern.edu.

CALGB 90601 A Randomized Double-Blinded Phase III Study Comparing Gemcitabine, Cisplatin, and Bevacizumab to Gemcitabine, Cisplatin, and Placebo in Patients with Advanced Transitional Cell Carcinoma

Transitional or urothelial cell carcinoma (TCC or UCC) is the most common form of bladder cancer and other cancers of the urinary tract. For more than 20 years, there have been no significant treatment advances for patients with metastatic TCC. It still remains the fourth most common cancer in men, and the fifth overall in the United States. New treatment options are needed, and improvements in first-line chemotherapy may improve overall survival for patients with this disease.

CALGB 90601 is an intergroup phase III study of gemcitabine and cisplatin with or without bevacizumab in patients with advanced TCC. The study seeks to determine if the addition of VEGF inhibition will improve overall survival in patients treated with standard cytotoxic (first-line) chemotherapy. Researchers have found that angiogenesis plays a critical role in TCC growth and progression. When signaling molecules, such as vascular endothelial growth factor (VEGF), bind to receptors on the surface of normal endothelial cells it results in signaling within the cells that promotes the growth and survival of new blood vessels. The vessels deliver oxygen and nutrients to the cancer which leads to tumor expansion and metastases.

Phase II study data of the three-drug regimen (gemcitabine, cisplatin and bevacizumab) showed a promising median overall survival of 19 months as compared to the historical experience of 14 months with chemotherapy alone. These data provide the rationale for the testing of this regimen.

Recently, the eligibility criteria for the study were

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Study Details
CALGB 90601

- Study PI: Jonathan Rosenberg, MD
- Targeted enrollment of 500 patients
- Primary study endpoint: overall survival (OS); secondary endpoints: progression-free survival (PFS), objective response rate, and toxicity
- Endorsed by SWOG and ECOG, and open for accrual through the CTSU

modified to allow inclusion of patients with creatinine clearance greater than or equal to 50 ml/minute to enroll using a modified split-dose regimen. The study includes maintenance therapy with bevacizumab or placebo following the completion of six cycles of chemotherapy. Critical translational questions are also being addressed in the study such as the role of germ-line alterations in predicting outcomes, the impact of DNA damage response proteins in chemotherapy resistance, and the impact of tobacco use on cancer outcomes. Specimens collected in this trial will create one of the largest prospectively collected, tumor and blood repositories of uniformly treated patients with transitional cell carcinoma. The samples will be available to Alliance and other investigators who propose concepts to further explore the biology of this disease.

The trial is reaching 50 percent of the accrual target. Monthly review of adverse events by the safety monitoring team has not revealed any significant signal of toxicity differences in the treatment arms.

The study protocol for CALGB 90601 can be found on the CTSU website (www.ctsu.org) with complete information on the trial design, patient eligibility and the treatment plan.

The Study Chair is Jonathan Rosenberg, MD, of the Memorial Sloan-Ketterning Cancer Center, e-mail: rosenbj1@mskcc.org.

CALGB 90802 Randomized Phase III Trial Comparing Everolimus Versus Everolimus plus Bevacizumab for Advanced Renal Cell Carcinoma Progressing after Treatment with Tyrosine Kinase Inhibitors

Today, most patients diagnosed with metastatic or recurrent renal cell carcinoma (RCC) are treated first with a multi-targeted VEGFR-inhibitor such as sunitinib and sorafenib. Unfortunately, the vast majority of these patients will develop disease progression while receiving treatment with one or both of these agents. A recent placebo-controlled phase III study showed that everolimus, an mTOR inhibitor, dramatically improved progression-free survival (PFS) in patients whose disease progressed after one or more multi-kinase VEGFR-inhibitor therapies, thus establishing a new standard of care for patients in this setting.[1]

Bevacizumab and everolimus both carry the capacity to modulate the VEGF pathway and have independently been shown to have activity in RCC. The combination of these agents in the treatment of RCC is mechanistically rational. Additionally, the agents are easy to administer and have not been reported to cause overlapping toxicities which will improve the likelihood of successful long-term drug administration.

CALGB 90802 is an intergroup phase III trial that seeks to determine whether everolimus plus bevacizumab is more effective than everolimus alone in the treatment of patients with advanced RCC who

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have progressed on tyrosine kinase inhibitors. This study continues the Alliance's successful exploration of rational combinations for the treatment of advanced RCC, and advances knowledge of the biologic basis for the disease and its therapy. There are three correlative science substudies included in CALGB 90802 to study plasma-, urine- and tissue-based biomarkers and pharmacogenomics.

In response to investigator feedback, the study design was amended in May 2012 to remove the placebo infusions which was reported to be a barrier for patient enrollment. The study is now an open-label trial. The primary endpoint, stratification factors and the total number of patients enrolled in this study will not change.

The study protocol for CALGB 90802 can be found on the CTSU website (www.ctsu.org) with complete information on the trial design, patient eligibility and the treatment plan.

Study Details
CALGB 90802

- Study PI: George Philips, MBBS, MD, MPH, FACP
- Targeted enrollment of 700 patients
- Primary study endpoint: overall survival (OS); secondary endpoints: progression-free survival (PFS), objective response rate (defined as confirmed CR plus PR), and toxicity
- Endorsed by SWOG, and open for accrual through the CTSU

The Study Chair is George Philips MBBS, MD, MPH, FACP, of Georgetown University Hospital, e-mail: george.k.philips@gunet.georgetown.edu.

Source

1. Motzer RJ, Escudier B, Oudard S et al. Efficacy of everolimus in advanced renal cell carcinoma:a double blind, randomized, placebo-controlled phase III trial. Lancet 2008;372:449-456.

Alliance Members on the Move

Lucile L.Adams-Campbell

The National Institute on Minority Health and Health Disparities, a part of the U.S. Department of Health and Human Services' National Institutes of Health, has awarded a $6.1 million grant over the next five years to Georgetown University Medical Center (GUMC) to establish the Center of Excellence for Health Disparities in Washington, DC. **Lucile L. Adams-Campbell, PhD,** Associate Dean for Community Health and Outreach for GUMC, is a Co-Principal Investigator of the grant. Dr. Adams-Campbell is also Associate Director for Minority Health and Health Disparities Research at Georgetown Lombardi Comprehensive Cancer Center.

Richard L. Schilsky

Richard L. Schilsky, MD, Professor of Medicine and Section Chief of Hematology/Oncology at the University of Chicago Department of Medicine, was recently named recipient of the 2012 Bob Pinedo Cancer Care Prize. The $50,000 award, presented by the Society of Translational Oncology (STO), recognizes Dr. Schilsky's clinical and research leadership in the areas of gastrointestinal cancers and cancer pharmacology coupled with his compassionate care of cancer patients. It will be presented at the third annual STO meeting, to be hosted by UNC Lineberger Comprehensive Cancer Center at the Rizzo Center in Chapel Hill, NC, October 20-21, 2012.

Upcoming Alliance Meeting / Registration Now Open

2012 Fall Committee Meetings

Open to Alliance committee members only

November 15-17, 2012
InterContinental Chicago O'Hare
Rosemont, IL 60018

Registration is now open for Alliance committee members. By now, individuals should have received a meeting invitation by e-mail.

For travelers funded by the Alliance Office of the Group Chair:

- Check individual meeting invitation for specific instructions.
- Make room reservations through the online registration site.
- Book your flights early using Egencia, the official travel agency of the Alliance for Clinical Trials in Oncology.

NOTE

- The Alliance Neuro-Oncology Committee will not meet at the 2012 Fall Committee Meetings. It will meet at the Society for Neuro-Oncology (SNO) meeting in Washington, DC, on Thursday, November 15, 4:30-7:30 pm, in the Columbia 1 meeting room at the Washington Hilton Hotel.
- See Alliance website for meeting schedule

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

For more information on the Alliance and updates to meeting information, visit allianceforclinicaltrialsinoncology.org