Alliance for Clinical Trials in Oncology
NEWS
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SPOTLIGHT ON TRIALS

Alliance, NCI Networks Launch Integrated Lung Cancer Trials Called ALCHEMIST

Trials to screen for uncommon genetic features in patients with early-stage lung cancer and help determine better treatment options for patients

The Alliance for Clinical Trials in Oncology, in conjunction with the National Cancer Institute (NCI) and ECOG-ACRIN Cancer Research Group, recently launched the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials, or ALCHEMIST – three trials to identify patients with early-stage lung cancer who have tumors that contain uncommon genetic changes and evaluate whether drug treatments aimed at those changes can improve their survival. As lead network group, the Alliance is coordinating two of the three trials, including the ALCHEMIST screening trial and the adjuvant treatment trial for patients with epidermal growth factor receptor (EGFR) mutations. All of the NCI-supported National Clinical Trials Network (NCTN) groups are participating in the trials.

The three trials of ALCHEMIST are:

ALCHEMIST - Screening component (A151216)
Coordinated by the Alliance | Principal Investigators: Pasi A. Jänne, MD, PhD and Geoffrey Oxnard, MD

ALCHEMIST - EGFR Treatment component (A081105)
Coordinated by the Alliance | Principal Investigator: Ramaswamy Govindan, MD

ALCHEMIST - ALK Treatment component (E4512)
Coordinated by ECOG-ACRIN | Principal Investigator: David Gerber, MD

Participants enrolled in ALCHEMIST need to have been diagnosed with lung adenocarcinoma or other types of non-squamous, non-small cell lung cancer (or NSCLC), and must be planning to undergo surgery or have already undergone surgical removal of their tumors.

In the ALCHEMIST screening trial, tissue from the participant's surgical resection will be tested in a central laboratory for genetic changes in two specific genes – EGFR and anaplastic lymphoma kinase (ALK). Participants with tumors found to contain EGFR mutations or rearrangement in the ALK gene will then be referred to one of the two randomized, placebo-controlled treatment trials evaluating specific drugs targeted against these genetic alterations, erlotinib and crizotinib, respectively. These drugs have been approved by the U.S. Food and Drug Administration (FDA) in the treatment of advanced non-small cell lung cancer in patients whose tumors contain the targeted molecular alterations; however, it is not known if these drugs will be beneficial for patients with early-stage disease. Those participants that receive standard therapy after their surgery (consisting of chemotherapy with or without radiation therapy, as prescribed by their treating physicians) will complete the therapy prior to participating in the ALCHEMIST treatment trials.

"We are excited to participate in this ambitious undertaking led by the Alliance, in collaboration with the NCI and NCTN," said Geoffrey Oxnard, MD, co-principal investigator of the screening component (A151216). "Through this large scale collaborative effort to genotype thousands of early-stage lung cancer patients, ALCHEMIST

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Alliance Study Explores Adjuvant Treatments in Recurrent GBM to Extend Overall Survival

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 Resective Recurrent Glioblastoma Multiforme (GBM)

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 4 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 recurrent GBM patients, with notable treatment related toxicities including wound breakdown after surgical resection.[6]

There is an unmet medical need for highly specific and non-toxic adjuvant therapy to treat recurrent GBM patients undergoing surgical resection. Immunotherapy is an appealing method to specifically target tumor cells in glioma patients, while minimizing adverse treatment effects.[7] There is evidence of immune mediated processes involved in GBM: antigens in the CNS lead to production of cytotoxic T cells and antibody response. Also, antigen specific T cells are seen in CNS tumors, and microglia and macrophages act as antigen presenting cells in the CNS. CNS tumors themselves cause immunosuppression, as evidenced by low lymphocyte counts, low antigen and mitogen responses, and T cells with impaired function. Any immunotherapy undertaken must overcome this. One way to overcome this is to resect tumor, as this decreases steroid requirement and the decrease in tumor bulk helps to downregulate the immunosuppression caused by the tumor.[7]

Several methods have been used successfully to evoke anti-tumor immunity in GBM patients, with evidence of peripheral and site-specific immune responses. Heat Shock Protein-Peptide Complex-96 (HSPPC-96)

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ALCHEMIST Trials

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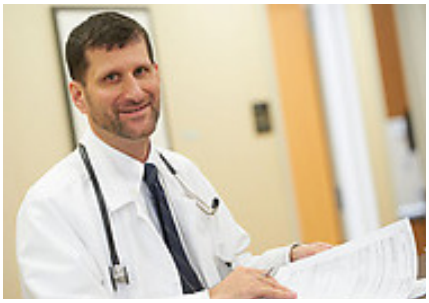
allows us to test better adjuvant treatments while simultaneously teaching us important lessons about the genetic complexity of lung cancer."

Approximately 10 percent of patients in the U.S. with non-squamous NSCLC will have tumors with alterations in the EGFR gene and five percent will have alterations in the ALK gene. ALCHEMIST will screen about 6,000 to 8,000 potential participants at hundreds of sites across the U.S. over five to six years in order to identify those with EGFR and ALK alterations that would be eligible for the treatment trial, resulting in about 800 patients being enrolled in the two ALCHEMIST treatment trials. All screened participants, irrespective of the marker (EGFR, ALK) status of their tumors, will be followed for a period of five years in the screening trial. At the conclusion of the trials, statisticians will analyze the survival benefit of patients who received the additional targeted drug therapy to patients who received standard therapy alone.

"If molecularly targeted drugs for EGFR and ALK prolong patient survival in the adjuvant setting, ALCHEMIST participants will be among the first lung cancer patients to benefit from the addition of a molecularly targeted lung cancer treatment following potentially curative surgical resection," said Ramaswamy Govindan, MD, principal investigator of the EGFR treatment component (A081105). "This will also provide infrastructure to test other emerging targeted therapies in appropriately selected patients with completely resected lung cancer."

ALCHEMIST trials are currently recruiting participants. Refer to the study protocols, which can be found on the CTSU menu (ctsu.org) and the Alliance website at AllianceforClinicalTrialsinOncology.org, for complete information on the trial design, treatment plan and patient eligibility.



Attacking AR Axis, Improving Outcomes, and Preparing for the End of OS as an Interpretable Clinical Trial Endpoint

By Michael J. Morris, MD
Memorial Sloan Kettering Cancer Center
Chair, Alliance Genitourinary (GU) Committee

The treatment of castration-resistant metastatic prostate cancer (mCRCP) has undergone more changes in standards of care in the past four years than some solid tumors have seen in as many decades. These therapies represent a wide spectrum of drugs classes that prolong life in patients who, not long ago, faced the unfortunate prospect of having no treatments that conferred a survival benefit. Recent U.S. Federal Drug Administration (FDA) approvals for new life-prolonging drugs for mCRPC include drugs that are cytotoxics, vaccines, second-generation anti-androgens, androgen biosynthesis inhibitors, and bone-targeted alpha-emitting radiopharmaceuticals.[1-6]

This dynamic environment has created an extensive array of treatment opportunities for prostate cancer patients with mCRCP. Yet, this abundance of options has also challenged clinicians and investigators to understand how to optimize these therapies in regard to timing, sequence, and combination. The Alliance GU Committee has been particularly sensitive to filling this medical need, especially in regards to treatment that targets the androgen receptor (AR) axis, in which our committee has an especially long and rich history. We were pioneers in examining AR signaling, exploring the anti-androgen withdrawal phenomenon, first generation androgen biosynthesis inhibition (CALGB 9583), and first generation anti-androgens (CALGB 9782).[7,8]

Both abiraterone and enzalutamide have significantly altered the armamentarium for mCRPC. Both drugs are well tolerated, administered orally, and significantly improve progression free survival and overall survival in men with mCRPC, both before and after chemotherapy.[1,6,9] Nonetheless, patients do progress on these drugs as single agents, after a median of approximately 14 months and 16 months for abiraterone and enzalutamide respectively in the pre-chemotherapy setting. Once patients progress on one agent, they infrequently derive significant benefit from the other. Mechanisms of acquired and primary resistance include increasing tumoral androgen levels, AR overexpression, and others.[10]

The underlying hypothesis of Alliance A031201 is that administering both drugs concurrently will maximally block the AR axis prior to the acquisition of resistance mechanisms, and improve on outcomes seen with the usual sequential approach. In designing the trial, we made some educated assumptions: that enzalutamide would demonstrate a survival benefit in the pre-chemotherapy setting (an assumption that has turned out to be correct), and that it would become the more common choice for first line therapy for mCRPC. Alliance A031201 therefore uses enzalutamide alone as a control arm. The investigational arm is enzalutamide and abiraterone with prednisone. The study will accrue 1,224 patients, involves a 1:1 randomization, has a primary endpoint of overall survival, and is powered to detect a hazard ratio of 0.77 in favor of the combination arm. This trial, if positive, will change how first-line therapy for mCRPC is treated. The trial explores a host of correlative biomarkers, including the predictive value angiokine markers (building on our committee's work on our previous trial of mCRPC, CALGB 90401), pre-treatment androgen levels, pre- and post-treatment RNA and micro-RNA detection, PK assessments, pharmacogenomic studies, and optimization of imaging response biomarkers.

Correlatives that relate to response assessments are particularly crucial to future drug development in prostate cancer. As the number of therapies that improve overall survival for mCRPC increases, the number of post-protocol treatments that can obscure overall survival (OS) for a given trial commensurately amplifies as well. Informative interim endpoints with strong clinical correlation are a major need in this disease, and a significant focus of our Committee. We have a companion Biomarker, Imaging and Quality of Life Studies Funding Program (BIQSFP) grant to study imaging endpoints in the Alliance A031201, in collaboration with the Alliance Imaging Committee, to further refine current response assessments and their relationship to OS. It is our hope that this trial, and the science embedded in it, will not only define tomorrow's standard of care for first line therapy for mCRPC, but clarify how future drugs might be better and more efficiently tested in the field as a whole.

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Buckner

Buckner to Lead Alliance NCORP Base

The National Cancer Institute (NCI) has awarded the Alliance for Clinical Trials in Oncology a five-year, $47.5 million grant to lead its NCI Community Oncology Research Program (NCORP) Research Base. **Jan C. Buckner, MD**, is the Contact Principal Investigator and Director of the Alliance Cancer Control Program (CCP). He is also Chair of the Department of Oncology and Deputy Director of Cancer Practice at Mayo Clinic Cancer Center in Rochester, MN.

Paskett

Electra D. Paskett, PhD, is also Principal Investigator on this award. Dr. Paskett is Deputy Director of the Alliance Cancer Control Program and Director of the Cancer Control Program at The Ohio State University Comprehensive Cancer Center in Columbus, OH. She is also Chair of the Alliance Health Disparities Committee and a member of the Alliance Prevention Committee and Alliance Symptom Intervention Committee within the CCP. In addition, Dr. Paskett is Co-Principal Investigator of the CALGB CCOP research base grant, which ends in 2015.

NCORP is a national network of cancer investigators, cancer care providers, academic institutions and other organizations that provides care to diverse populations in community-based health care practices across the United States. NCORP research bases will design and conduct cancer prevention, cancer control, cancer screening and post-treatment surveillance clinical trials.

The Alliance NCORP Research Base will be one of seven research bases across the country that will design and conduct multicenter cancer clinical trials and cancer care delivery research. NCORP research bases will also provide overall administration, data management, scientific leadership, and regulatory compliance for their trials.

In addition to the seven research bases, NCORP includes 34 community sites and 12 minority/underserved community sites that will accrue participants to clinical trials conducted by NCORP research bases, NCI National Clinical Trials Network (NCTN) treatment and imaging trials, quality-of-life studies, and cancer care delivery research involving patients, practitioners, and health care organizations. NCORP minority/underserved community sites have a patient population comprising at least 30 percent racial and ethnic minorities or rural residents.

NCORP replaces two previous NCI community-based clinical research programs: the NCI Community Clinical Oncology Program (CCOP), made up of the Community Clinical Oncology Programs, Minority-Based Clinical Oncology Programs, and Research Bases, and the NCI Community Cancer Centers Program (NCCCP).

Resources Available to Alliance Members

The Alliance NCORP Research Base is now providing support and resources to researchers at Alliance member institutions for Alliance investigator-initiated trials in the following areas: assistance with clinical trial concept development, protocol development, data management, quality control, statistical support, biospecimen collection, and assistance with patient accrual or access to existing data sets

To learn more about these NCORP resources, contact Jacqueline Lafky, Program Manager for the Alliance Cancer Control Program by e-mail: lafky.jacqueline@mayo.edu

For more information on the Alliance NCORP Research Base, contact Jan Buckner, MD, by e-mail: buckner.jan@mayo.edu

Hunt to Lead ACS Clinical Research

Hunt

The Alliance Board of Directors recently announced the appointment of **Kelly K. Hunt, MD, FACS**, to the position of Director of the American College of Surgeons Clinical Research Program. This program is the home of Cancer Care Delivery Research (CCDR) for the Alliance, and also involves an important collaboration with the Commission on Cancer and the American College of Surgeons. Dr. Hunt replaces **Heidi Nelson, MD**, who was appointed in 2011 as the program's first director within the newly formed Alliance. Dr. Nelson is the Fred C. Andersen Professor and Vice Chair for Research in the Department of Surgery at Mayo Clinic.

Nelson

Under Dr. Nelson's leadership, the ACS Clinical Research Program through its initial four committees (Member Services, Education, Cancer Care Standards Development and Research Development), developed unique research programs, including projects centered on comparative effectiveness research and emerging technology research. She played a significant role in the formation of the CCDR Committee, which represented the reformulation of the Comparative Effectiveness Research Committee (formerly part of the Alliance Cancer Control Program).

Dr. Hunt is Hamill Foundation Distinguished Professor in honor of Dr. Richard G. Martin, Sr. at the University of Texas MD Anderson Cancer Center. She also serves as the Chief of the Breast Surgical Oncology Section in the Department of Surgical Oncology. Dr. Hunt joined the Alliance from the American College of Surgeons Oncology Group, where she served on the Executive Committee and as the Chair of the Breast Organ Site Committee. In addition to membership on the Alliance Executive Committee, Dr. Hunt has chaired the Cancer Care Standards Development Committee and served as Vice-Chair of the Breast Committee.

Dr. Hunt is an international leader in the treatment of breast cancer and soft tissue sarcomas, and her research involves development of prognostic and predictive factors for improving cancer staging and treatment response.

Group Vice Chair Leads by Example

Perez

Alliance Group Vice Chair **Edith A. Perez, MD**, is an internationally known translational researcher and cancer specialist. She is the Deputy Director At Large for Mayo Clinic Cancer Center based in Florida, and the Serene M. and Frances C. Durling Professor at Mayo Clinic College of Medicine. She also serves as Chair of the Mayo Clinic Breast Cancer Translational Genomics Program and the Breast Cancer Specialty Council.

Within the Alliance, Dr. Perez also serves as Chair of the Publications Committee. As an Alliance researcher, she is developing a wide range of clinical trials exploring targeted therapeutic agents for the treatment and prevention of breast cancer. Much of her work focuses on the study of compounds designed to fight HER2-positive breast cancer and mentoring junior investigators. She is leading studies to evaluate the role of genetic biomarkers in the development, aggressiveness and therapeutic efficacy of therapies for breast cancer. This work has a strong significance for patients.

"The goal is to enhance the understanding of biological markers and pathways that drive breast cancer growth and development, as well as speed up access to personalized therapies," she said. "This joint commitment reinforces the pursuit to advance understanding of cancer genomics and improve patient care."

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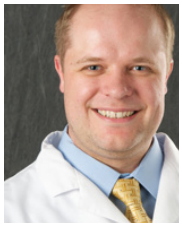
Alliance Investigator Receives ASTRO Award


Allen

An Alliance investigator is one of two junior faculty to receive an award from the American Society for Radiation Oncology (ASTRO) to advance radiation oncology research at its annual meeting held recently in San Francisco, CA.

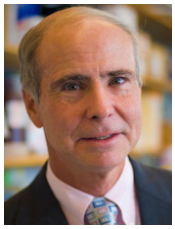
Bryan G. Allen, MD, PhD, of University of Iowa Hospitals and Clinics, has received the 2014 ASTRO Junior Faculty Career Research Training Award. Dr. Allen is working to determine if pharmacological ascorbate can be used to modulate chemoradiation sensitivity in non-small cell lung cancer and therefore be utilized to improve outcomes in lung cancer treatment.

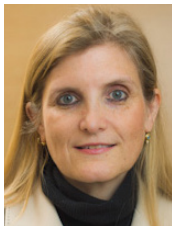
The award provides $100,000 annually for two years to two winners ($200,000 to each recipient) to support the careers of promising junior faculty by offering them the opportunity for dedicated time to work on research projects in radiation oncology, biology, physics or outcomes/health services. Recipients must be board eligible physicians, physicists in radiation oncology or radiobiologists within the first three years of their junior faculty appointment.

Alliance Members on the Move


Pisters


Adams-Campbell


Anderson


Schrag

Peter W.T. Pisters, MD, currently Vice President of the University of Texas MD Anderson Cancer Center's Regional Care System, has been recently appointed to serve as President & CEO of University Health Network (UHN). He is an internationally known tenured Professor of Surgery at MD Anderson. Dr. Pisters assumes his new role on January 1, 2015.

Lucille L. Adams-Campbell, PhD; **Kenneth C. Anderson, MD;** and **Deborah Schrag, MD, MPH**, have been named to the Institute of Medicine's (IOM) National Cancer Policy Forum.

The forum serves as a focal point and trusted venue for the engagement of national leaders from multiple sectors working cooperatively to address high priority policy issues in the nation's effort to combat cancer. The IOM draws upon its uniquely independent status and expertise to steward sustained discussion and collaboration among national experts and health stakeholders on issues relevant to the goals of preventing and treating cancer.

Dr. Anderson is Program Director, Jerome Lipper Multiple Myeloma Center and LeBow Institute for Myeloma Therapeutics, and Kraft Family Professor of Medicine at Harvard Medical School. Dr. Adams-Campbell is Associate Director for Minority Health and Health Disparities Research, Associate Dean for Community Health and Outreach, and Professor of Oncology at Lombardi Comprehensive Cancer Center at Georgetown University Medical Center. Dr. Shrag is Professor, Department of Medicine, Harvard Medical School and Chief, Division of Population Sciences, Medical Oncology at the Dana-Farber Cancer Institute.

Alliance Institutions Among Top-Ranked Hospitals for Cancer in the United States

More than 25 Alliance institutions, including medical centers and hospitals, rank among the 50 top-scoring hospitals in the annual U.S. News & World Report Top-Ranked Hospitals for Cancer issue. About 900 hospitals are listed in the entire publication. All treat significant numbers of patients with cancer. A hospital is listed only if it treated at least 249 such inpatients in 2010, 2011 and 2012. Here are the Alliance institutions that graced the top 50 listed in order of rank.

#1	Memorial Sloan Kettering Cancer Center
#2	University of Texas MD Anderson Cancer Center
#3	Mayo Clinic Rochester
#4	Dana-Farber/Brigham and Women's Cancer Center
#7	Massachusetts General Hospital
#8	UCSF Medical Center
#13	Cleveland Clinic
#14	New York-Presbyterian University Hospital of Columbia and Cornell
#15	University of Colorado Hospital
#16	Moffitt Cancer Center
#20	Wake Forest Baptist Medical Center
#21	Barnes-Jewish Hospital/Washington University
#22	Duke University Hospital
#25	UC San Diego Medical Center
#26	Mayo Clinic Arizona
#27	University of Iowa Hospitals and Clinics
#29	University of Kansas Hospital
#30	Ohio State University James Cancer Hospital
#31	University of Chicago Medical Center
#31	UPMC-University of Pittsburgh Medical Center
#33	Oregon Health and Science University Hospital
#34	University of Michigan Hospitals and Health Centers
#36	Nebraska Medical Center
#37	Hackensack University Medical Center
#38	University of North Carolina Hospitals
#43	University of Wisconsin Hospital and Clinics
#45	Florida Hospital Orlando
#46	University of Maryland Medical Center
#47	Loyola University Medical Center
#48	Mount Sinai Hospital

Update in GU Oncology

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Sources

1. Ryan CJ, Smith MR, de Bono JS, et al: Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 368:138-48, 2013.
2. de Bono JS, Logothetis CJ, Molina A, et al: Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 364:1995-2005, 2011.
3. Parker C, Nilsson S, Heinrich D, et al: Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 369:213-23, 2013.
4. de Bono JS, Oudard S, Ozguroglu M, et al: Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 376:1147-54, 2010.
5. Kantoff PW, Higano CS, Shore ND, et al: Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 363:411-22, 2010.
6. Scher HI, Fizazi K, Saad F, et al: Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 367:1187-97, 2012.
7. Small EJ, Halabi S, Dawson NA, et al: Antiandrogen withdrawal alone or in combination with ketoconazole in androgen-independent prostate cancer patients: a phase III trial (CALGB 9583). J Clin Oncol 22:1025-33, 2004.
8. Monk JP, Halabi S, Picus J, et al: Efficacy of peripheral androgen blockade in prostate cancer patients with biochemical failure after definitive local therapy: results of Cancer and Leukemia Group B (CALGB) 9782. Cancer 118:4139-47, 2012.
9. Beer TM, Armstrong AJ, Sternberg CN, et al: Enzalutamide in men with chemotherapy-naive metastatic prostate cancer (mCRPC): Results of phase III PREVAIL study. J Clin Oncol 32 2014.
10. Courtney KD, Taplin ME: The evolving paradigm of second-line hormonal therapy options for castration-resistant prostate cancer. Curr Opin Oncol 24:272-7, 2012.

New: ACS 2014 Outcomes Research Course

The American College of Surgeons (ACS) Surgical Research Committee will sponsor the sixth biennial Outcomes Research Course, December 4-6, at ACS headquarters in Chicago, IL. Course participants will select modules appropriate to their skill level and interest. The course, designed for clinical and health service researchers at all levels of experience, will focus on didactics and skills-based labs in managing, analyzing, and interpreting large datasets. In addition, participants will have the opportunity to present their research to experts for critique and advice.

The ACS designates this live activity for a maximum of 21.5 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity. For more information about the Outcomes course, please visit https://www.facs.org/quality-programs/about/cqi/education/outcomes-research-course. You can register online at https://www.thinkreg.com/coral/viewWebsite.do?siteId=8a94a8b4473684ee01475b69909f0be3

For more information, e-mail: OutcomesResearchCourse@facs.org.

Available Now: Updated Material from PMB

The following new and updated materials are available on the NCI's Pharmaceutical Management Branch (PMB) web page http://ctep.cancer.gov/branches/pmb:

Agent Management

- Policy and Guidelines for Investigational Agent Distribution (UPDATED)
- Policy and Guidelines for Investigational Agent Transfers (UPDATED)
- Policy and Guidelines for Investigational Agent Returns (UPDATED)

FAQ

- Returning agent to NCI Clinical Repository (UPDATED)

PMB is in the process of recording Investigational Drug Accountability training videos. The following videos will soon be available through PMB's website and linked to the NCI YouTube channel https://www.youtube.com/user/NCIgov/:

Did You Know? This Publications Tip

Q: How does the National Institutes of Health (NIH) determine the official date of publication?

A: NIH determines the official date of publication for the public access policy based on information received from the publisher and the National Library of Medicine (NLM). The official date of publication can be found in the PubMed citation display for a paper immediately after the journal title abbreviation.

NIH uses the official date of publication for determining the public access compliance status of a paper and calculating when a paper should be made public on PubMed Central. Papers with an NIHMSID or published in PMC participating journals (submission Methods A and B) will be listed as provisionally compliant in My Bibliography until a publication date is determined. An "epub ahead of print" date for a citation in PubMed is not considered the official date of publication, and these papers are still considered in press.

Note that when only partial publication dates are available (e.g. Month and Year, Season and Year), NLM calculates the date as the first date of that time period (e.g. March 2013 = March 1, 2013). See http://www.nlm.nih.gov/bsd/licensee/elements_article_source.html for additional information about NLM dates.

Recurrent GBM Trial

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consists of the heat shock protein glycoprotein-96 (HSP gp-96) and a wide array of chaperoned proteins, including autologous antigenic peptides. Heat shock proteins (HSP) are molecules that respond to cellular stress and counteract abnormal protein folding. They are known to modulate immune responses, especially the HSP gp-96. In a stressful environment, such as a tumor, HSPs are upregulated and highly expressed on tumor cells. This protects the tumor and leads to resistance to therapy. HSP expression is associated with cellular proliferation, apoptosis evasion, tissue invasion, metastasis, and angiogenesis with kidney cancer.

HSPPC-96 immunization works mechanistically by interacting with antigen presenting cells (APCs) via specific receptors, including CD91.[8, 9] The highly specific nature of the interaction between HSPPC-96 and APCs is a significant advantage over other cancer vaccine approaches; and has been shown to facilitate robust CD4+ and CD8+ T-cell immune responses.

Based on these positive preliminary findings, a large randomized trial, incorporating the current best available treatment (bevacizumab), in recurrent GBM is warranted. Furthermore, there is a theoretical scientific basis for potential synergies between bevacizumab and a specific active immunotherapy such as HSPPC-96.

In Alliance A071101, the primary objective is to demonstrate that patients with recurrent GBM randomized to HSPPC-96 plus bevacizumab arms – either received concomitantly (Arm 1) or given at the time of progression (Arm 2) - have improved overall survival as compared to patients who were randomized to bevacizumab alone arm (Arm 3). In other words, Arms 1 and 2 will be combined and then compared to Arm 3 to explore the additive effect of HSPPC–96. About 222 people will take part in this study.

Alliance A071101 is an important study 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 affords the opportunity to also 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. As such, this trial 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.

Alliance A071101 is currently recruiting participants. Refer to the study protocol, which can be found on the Alliance website at www.AllianceforClinicalTrialsinOncology.org, for complete information on the trial design, treatment plan and patient eligibility. The Alliance Study Chair is Andrew Parsa, MD, PhD, Northwestern University, e-mail: aparsa@nmff.org

Sources

1. Stupp, R., et al., Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med, 2005. 352(10): p. 987-96.
2. Lamborn, K.R., S.M. Chang, and M.D. Prados, Prognostic factors for survival of patients with glioblastoma: recursive partitioning analysis. Neuro Oncol, 2004. 6(3): p. 227-35.
3. Brem, H., et al., Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group. Lancet, 1995. 345(8956): p. 1008-12.
4. Friedman, H.S., et al., Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol, 2009. 27(28): p. 4733-40.
5. Cohen, M.H., et al., FDA drug approval summary: bevacizumab (Avastin) as treatment of recurrent glioblastoma multiforme. Oncologist, 2009. 14(11): p. 1131-8.
6. Clark, A.J., et al., Impact of bevacizumab chemotherapy on craniotomy wound healing. J Neurosurg, 2011. 114(6): p. 1609-16.
7. Heimberger, A.B. and J.H. Sampson, Immunotherapy coming of age: what will it take to make it standard of care for glioblastoma? Neuro Oncol, 2011. 13(1): p. 3-13.
8. Binder, R.J. and P.K. Srivastava, Essential role of CD91 in re-presentation of gp96-chaperoned peptides. Proc Natl Acad Sci U S A, 2004. 101(16): p. 6128-33.
9. Binder, R.J., D.K. Han, and P.K. Srivastava, CD91: a receptor for heat shock protein gp96. Nat Immunol, 2000. 1(2): p. 151-5.

Group Vice Chair
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Dr. Perez has authored nearly 700 research articles in journals, books and abstracts. Her recent publications include those on two Alliance studies: NCCTG 9881 (*J Cancer. 2014 Sep 9; 111(6):1065-71. Epub 2014 Aug 12.*) and CALGB 40101 (*J Clin Oncol. 2014 Aug 1; 32(22):2311-7. Epub 2014 Jun 16*).

An avid runner, Dr. Perez leads 26.2 with Donna: The National Marathon to Finish Breast Cancer, which funds breast cancer research and treatment. The marathon, based in Jacksonville, has raised nearly $4 million in its seven-year existence.

Next Meeting Date

2014 Alliance Fall Group Meeting | November 5-8 | Chicago, IL
Registration is now open.

Travelers who are directly funded by the Alliance should have received an invitation by e-mail to register for the meeting. For updates, visit the Alliance website at www.AllianceforClinicalTrialsinOncology.org

Upcoming Alliance Meetings

2015 Summer Group Meeting | May 14-16
2016 Fall Group Meeting | November 2-5
2017 Fall Group Meeting | November 1-4

All meetings are open to all Alliance members and will be held at Loews Chicago O'Hare, 5300 N. River Road, Rosemont, IL 60018

For meeting and travel inquiries,
contact Alison Lewandowski
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phone: 617-525-3022

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