Committee Spotlight: Head and Neck Cancer Committee Is Highly NRG-ized!

Quynh-Thu Le, MD, NRG Oncology Head and Neck Cancer Committee Chair

A cadre of dedicated investigators, exceptional statistical and operational support, and guidance from NRG Oncology and National Cancer Institute leaders are key components of the highly productive NRG Oncology Head and Neck Cancer Committee according to Quynh-Thu Le, MD, committee chair and chair of the Department of Radiation Oncology at the Stanford University School of Medicine. “We have a tremendously engaged head and neck cancer research community that has supported strong study participant accrual, the development of new and innovative trials, and results reporting,” says Le.

The work of this multidisciplinary research community is exemplified by the activation of two head and neck cancer protocols this year. The NRG-HN001 trial, which was activated in April, explores the use of Epstein Barr virus DNA as a biomarker for selecting patients most appropriate for adjuvant chemotherapy after concurrent chemoradiation. This trial also aims to see whether adjuvant chemotherapy regimens other than the current standard of care will benefit a subset of patients with locoregionally advanced nasopharyngeal carcinoma who are at high risk for cancer recurrence. “This is truly a trail-blazing trial for us, as it’s one of the first biomarker-driven trials to individualize a patient’s treatment strategy,” says Le, who notes that conducting biomarker-driven, multimodality research is a major aim of the committee. “We can no longer treat all head and neck cancers in the same way; we now have solid evidence that these cancers are heterogeneous.”

The NRG-HN002 trial, which was activated in October, is another example of a clinical trial evaluating individualized treatment based on the results of biomarker analysis. Led by Sue S. Yom, MD, PhD, an associate professor in the departments of radiation oncology and otolaryngology-head and neck surgery at the University of California, San Francisco, this trial seeks to define new, less-intensive treatment options for patients with human papillomavirus (HPV)-positive oropharyngeal cancer who are at low risk for cancer recurrence (read press release).

These two new NRG Oncology head and neck cancer trials build on the results of several past trials, with Le referring to the RTOG 0129 and RTOG 0522 studies as examples.

Registration Is Now Open for the NRG Oncology Semiannual Meeting in February!

Please plan to attend the NRG Oncology Semiannual Meeting scheduled for February 5–8, 2015. The NRG Oncology research community will once again gather at the Manchester Grand Hyatt in San Diego, California.

For registration details and more meeting information, visit NRG Oncology Semiannual Meeting.

NRG Oncology by the Numbers*

NRG Oncology’s cancer research enterprise includes thousands of investigators carrying out research at sites around the globe. The following statistics provide a glimpse of the group’s research scope.

- Número de ensayos en los que participa NRG Oncology: 108
- Miembros de los Centros Académicos de Participación (LAPS): 29
- Número de ensayos conducidos por NRG Oncology: 9
- Miembros del Programa de Investigación de Oncología Comunitaria (NCORP): 40
- Número de ensayos en desarrollo: 27
- Sede internacional: 22

*As of October 31, 2014

NRG Oncology at SABCS

NRG Oncology researchers will present a total of 16 abstracts at the 2014 San Antonio Breast Cancer Symposium (SABCS) to be held December 9–13. Findings of the NSABP B-40 trial on the effect of adding bevacizumab to standard neoadjuvant chemotherapy, results of the International Breast Cancer Study Group (IBCSG) SOFT trial, and information on biomarkers for trastuzumab identified in NSABP B-31 are among the study findings NRG Oncology researchers will discuss during the abstract presentations. Preregistration and hotel reservation deadlines are November 14. Details can be found at the SABCS site.
NRG Oncology Moves Forward With Strong Record of Trial Activation

Since becoming engaged formally in clinical trial research on March 1, 2014, NRG Oncology has opened enrollment for 8 clinical trials. From August through October, 5 new trials have been activated—and one trial pre-activated—across 5 different disease site committees. The trials activated since the last update in the NRG Oncology Newsletter are highlighted below.

The NRG-LU001 trial (Randomized Phase II Trial of Concurrent Chemoradiotherapy +/- Metformin HCL in Locally Advanced NSCLC), activated on September 25, is the first to investigate whether the drug metformin, when added to standard concurrent chemoradiotherapy, can be well-tolerated and improve progression-free survival for patients with locally advanced non-small cell lung cancer (NSCLC). Metformin is used in the treatment of millions of diabetic patients worldwide. Research carried out in the laboratories of the NRG-LU001 investigators showed that metformin has antitumor and radiosensitizing activity in NSCLC at concentrations that are safe for nondiabetic patients.

“Retrospective studies have suggested that metformin may be able to improve the response of the epithelial tumors to cytotoxic therapy.”
THEODOROS (THEOS) TSAKIRIDIS, MD
NRG-LU001 Co-principal Investigator

“This study will examine whether we can improve chemoradiotherapy response with a well-tolerated and economical modifier of metabolism.”
HEATH D. SKINNER, MD, PHD
NRG-LU001 Co-principal Investigator

A phase III study evaluating radiotherapy in addition to chemotherapy for patients with inoperable, localized intrahepatic cholangiocarcinoma (IHC) was opened for patient enrollment on September 29. The NRG-GI001 trial will evaluate the value of adding liver-directed radiotherapy (RT) to the standard treatment of gemcitabine/cisplatin chemotherapy. Though a fairly rare gastrointestinal malignancy, IHC is on the increase in the United States and Asia and is a disease with a very dismal prognosis.

“Collaborative investigations at Massachusetts General Hospital and The University of Texas MD Anderson Cancer Center have suggested that radiotherapy is beneficial to patients with IHC. However, this is the first trial to test the benefit of liver-directed radiotherapy formally in this patient population.”
THEODORE S. HONG, MD
NRG-GI001 Principal Investigator

Two NRG Oncology clinical trials were activated on October 27. The phase II randomized trial NRG-BN001 is the first study to assess outcomes for patients with newly diagnosed glioblastoma (GBM) when treated using either dose-intensified photon intensity-modulated radiotherapy (IMRT) or dose-intensified proton beam therapy compared with standard-dose photon radiotherapy. The trial is also the first to evaluate rigorously the use of temozolomide—an oral radiotherapy sensitizing chemotherapeutic drug—in conjunction with dose-intensified radiotherapy.

“The predominant pattern of local tumor recurrence highlights the importance of investigating more-intensive local therapies for patients with newly diagnosed glioblastoma.”
MINESH P. MEHTA, MBCHB
NRG-BN001 Co-principal Investigator

The NRG-HN002 phase II clinical trial seeks to define new, less-intensive treatment options for patients with oropharyngeal cancer that tests positive for the human papillomavirus (HPV) using p16 as a surrogate biomarker for HPV positivity. Patients who develop HPV-associated OPC are more likely to be younger and healthier, with a briefer history of smoking. Because these patients most often have significantly improved survival subsequent to undergoing therapy at a young age, long-term treatment side effects present compelling quality-of-life (QOL) issues.

“The emerging low-risk oropharyngeal cancer classification offers an opportunity to develop appropriate therapeutic paradigms for the recently identified and distinct subtype of HPV-positive disease.”
SUE S. YOM, MD, PHD
NRG-HN002 Principal Investigator

Clinical Trial Focus
GOG 278: A Trial Studying Physical Function and Quality of Life Before and After Surgery in Patients With Stage I Cervical Cancer
Activated in October 2012, the GOG 278 trial is recruiting patients actively at nearly 80 research sites across the United States and in Canada and the Republic of Korea. The study will assess the impact of nonradical surgical treatment consisting of either conservative simple hysterectomy or cone biopsy (for fertility preservation), each with lymph node sampling, in women diagnosed with stage I cervical cancer.
Clinical Trial Highlights (continued)

This is the first study to collect multicenter trial data about whether the two non-radical surgical approaches—compared with radical hysterectomy, the standard surgical approach for early-stage cervical cancer—provide patient outcome benefits regarding bladder and bowel function, sexual health, fertility preservation, quality of life, and emotional well-being. In addition, the study will examine cancer recurrence rates in both treatment groups.

“We hope to establish that patients diagnosed with early-stage cervical cancer can be treated successfully with non-radical approaches and experience significantly fewer side effects than what has been documented for radical surgery. This is an important issue for determining the quality of cancer survivorship in this typically young patient population,” says the trial’s principal investigator, Allan Covens, MD, an affiliate scientist at Sunnybrook Health Sciences Centre in Toronto, Canada.

Emphasizing that patient enrollment is straightforward, Covens states, “We know in our hearts that radical hysterectomy is overkill for small cancers, so it’s very motivating to discuss another treatment option with patients who have small tumors.” He notes that the trial’s required margin status for loop electrosurgical excision procedure (LEEP) and cone biopsy is a potentially confusing eligibility criterion. “The patients need to have surgical excision margins that are clear of cancer but not of cervical intraepithelial neoplasia,” explains Covens. Noting that positron emission tomography (PET) is not an eligibility requirement, Covens discourages investigators from ordering PET scans due to the low yield and potential for false-positive results—particularly in patients immediately following a LEEP or cone biopsy.

Cervical cancer is one of the most common cancers in women younger than 40 years of age, with the vast majority of patients seeking cancer care within their local communities. “This trial for patients with early-stage cervical cancer is especially well suited to be carried out within a community cancer care setting. We encourage more research sites—especially those affiliated with the NCI’s National Community Oncology Research Program—to open this trial,” says NRG Oncology NCORP PI/Executive Committee Chair Joan L. Walker, MD, a gynecologic oncologist at the Peggy and Charles Stephenson Cancer Center at the University of Oklahoma Health Sciences Center in Oklahoma City.

As of October 31, nearly 50 of the trial’s target accrual goal of 600 patients have been enrolled. “I thank participating research sites for their recruitment efforts to date. It’s through their continued commitment to this trial that we can reach our target enrollment and gain the data necessary to help patients and doctors make the best treatment decisions possible,” says Covens.

Shout Out to Sites
Collecting information and preparing the extensive documentation required for submission of a protocol to an institutional review board (IRB) requires significant collaboration on the part of site research teams. Obtaining expeditious IRB approval is critical to beginning study participants enrollment, meeting accrual targets, and obtaining the research data necessary to answer important questions related to improving patient care.

We are pleased to recognize the research sites first to provide notice of IRB approval and first to enroll a study participant onto an NRG Oncology trial.

First Site to Provide IRB Notifications
NRG-BN001 WellSpan York Hospital Intermountain Medical Center
NRG-GI001 Cancer Research for the Ozarks NCORP
NRG-LU001 FirstHealth Moore Regional Hospital DeKalb Medical

First Site to Enroll a Study Participant
NRG-HN001 Stanford University Hospitals and Clinic
NRG-LU001 OSF Saint Francis Medical Center
From the NRG Oncology Gastrointestinal Cancer Committee

NSABP trial finds different patient-reported outcomes associated with SSS and APR in the treatment of rectal cancer

In a randomized controlled trial of neoadjuvant chemoradiotherapy in patients with resectable stage II-III rectal cancer, researchers in the NSABP R-04 trial found that patients who underwent abdominoperineal resection (APR) reported different symptoms than did those who underwent sphincter-sparing surgery (SSS).

Of 987 patients with data for planned analysis, 62% underwent SSS and 38% underwent APR. Two symptom scales were administered at baseline and at 1 year postoperatively—the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) and the European Organization for Research and Treatment of Cancer (EORTC) colorectal cancer-specific quality of life questionnaire (QLQ-CR38). EORTC QLQ-CR38 functional scale results demonstrated that patients undergoing APR reported worse body image at 1 year than did those undergoing SSS. Men undergoing APR reported worse sexual enjoyment at 1 year than did men undergoing SSS. EORTC QLQ-CR38 symptom scale scores showed that patients in the APR group reported worse micturition symptoms at 1 year than did those in the SSS group. Patients undergoing SSS reported worse gastrointestinal tract symptoms and more weight loss than did patients undergoing APR.

These results may be useful in counseling patients anticipating surgery for rectal cancer.


From the NRG Oncology Head and Neck Cancer Committee

Patients With Head and Neck Cancers Do Not Benefit From the Addition of Cetuximab to Standard Chemoradiotherapy

The addition of cetuximab to treatment with cisplatin and radiotherapy (RT) did not improve the outcome of patients with locally advanced (nonmetastatic) head and neck cancer (HNC) according to results of a phase III clinical trial conducted by the Radiation Therapy Oncology Group (RTOG) (now carrying out research as NRG Oncology). In a paper published online in the Journal of Clinical Oncology regarding the results of the RTOG 0522 trial, the authors advise against the routine use of cetuximab with cisplatin and RT due to the lack of improvement in tumor control or survival and the increase in acute side effects. As previous reports have shown, these results confirm that patients with human papillomavirus (HPV)-positive HNC have significantly better outcomes than patients with HPV-negative HNC (read press release).


Tumor Human Papillomavirus Status Is a Strong Predictor of Survival for Patients With Oropharyngeal Cancer Progressing After Initial Treatment

Prior studies have demonstrated that tumor human papillomavirus (HPV) status is a prognostic biomarker for oropharyngeal cancer (OPC), as seen by patients with HPV-positive OPC living significantly longer than patients with HPV-negative disease. Although patients with HPV-positive OPC have a positive prognosis, up to 25% of these patients experience eventual disease progression. Investigators analyzing data from two trials conducted by the Radiation Therapy Oncology Group (now conducting research as NRG Oncology) report that tumor HPV status is also a predictor of survival for patients with OPC whose disease has progressed.

In an article published this week in the Journal of Clinical Oncology, data from 181 patients with OPC for whom data on p16 (a surrogate marker of tumor HPV status) were available showed that patients with p16-positive OPC had significantly improved survival rates compared with patients with p16-negative OPC (2.6 vs. 0.8 years, respectively, at a median of 4 years after disease progression) (read press release).


From the NRG Oncology Translational Science Committee

An Analysis of 356 Tumor Specimens Shows p16 Expression Is Not a Reliable Indicator of Human Papillomavirus (HPV) in Oral Cavity, Hypopharynx, and Larynx Cancers

The expression of p16 in oropharyngeal squamous cell carcinoma (OPSCC) is a validated biomarker of HPV positivity. Patients with HPV-positive OPSCC have significantly better outcomes than those with HPV-negative OPSCC. The strong correlation between p16 expression and...
Featured Publications (continued)

HPV positivity led to the use of p16 expression as a biomarker for patient selection in clinical trials evaluating if patients with HPV-positive OPSCC can undergo less-intense therapy than standard-of-care treatment in an effort to reduce treatment-related side effects without negatively affecting survival outcomes.

Investigators, led by Christine H. Chung, MD, associate professor of oncology at Johns Hopkins University, evaluated the prognostic significance of p16 expression in oral cavity, hypopharynx, and larynx cancers, collectively referred to as non-OPSCC, in which HPV infection is less common. Their analysis employed two widely used tests—immunohistochemistry (IHC) for p16 expression and in situ hybridization (ISH) for HPV detection (read press release).


People in the News

Doctor Aghajanian Recognized for Research Contribution

Carol Aghajanian, MD, PhD, co-chair of the NRG Oncology Developmental Therapeutics Committee, is the recipient of the National Cancer Institute's 2014 Michaele C. Christian Oncology Development Lectureship and Award. The prestigious award recognizes the contributions of individuals to the development of novel agents for cancer therapy. This award was established by the Cancer Therapy Evaluation Program in 2007 to honor the 20-year NCI career of Michaele C. Christian (read full announcement).

White House names patient advocate Halpin-Murphy a “Champion of Change”

Pat Halpin-Murphy, a member of NRG Oncology’s Patient Advocacy Committee, has been named a Champion of Change by the White House for her work in advocating for women's health care and insurance coverage. Pat is the former chair of the NSABP Patient Advocacy Committee and founder of the Pennsylvania Breast Cancer Coalition (see news video).

Committee Spotlight (continued from page 1)

“Although these trials did not meet their primary end points, through the meticulous collection of study data and biospecimens, we nonetheless have learned a lot,” says Le. “These trial data have provided significant insight about HPV status and its impact on patients with newly diagnosed and recurrent disease. They have also provided important information for the design of future trials in head and neck cancer.” She points to the impact of recently published findings that are likely to result in the stratification of patients by HPV tumor status for all future clinical trials investigating new treatment approaches for recurrent oropharyngeal cancer (read press release).

As evidence that NRG Oncology investigators have been actively mining the data that the head and neck cancer trials have amassed, five publications have appeared in 2014 issues of the Journal of Clinical Oncology, with one in press...
A broad range of NRG Oncology research results were presented at this year’s American Society for Radiation Oncology (ASTRO) Annual Meeting, which took place September 14–17 in San Francisco. More than 25 presentations showcased the breadth of NRG Oncology research, including reports on (a) RTOG 0621 results showing that treatment with radiotherapy (RT), androgen suppression therapy, and docetaxel improves cancer control for men with high-risk prostate cancer (read press release); (b) promising bladder-sparing RT strategies for muscle-invasive bladder cancer (read press release); (c) the lack of a long-term negative impact of RT on lymphedema risk among women undergoing sentinel node biopsy versus axillary lymph node dissection (read abstract); and (d) the positive outcome of credentialing research sites participating in the NSABP B-51/RTOG 1304 trial (read abstract).

Among the meeting’s highlights was a plenary presentation by Principal Investigator Jeff Michalski, MD, MBA, who is chair of the NRG Oncology Radiation Oncology Committee and the Carlos A. Perez Distinguished Professor of radiation oncology at Washington University Medical School in St. Louis. In reporting the preliminary results of the RTOG 0126 trial, which evaluated higher-dose (79.2 Gy) RT vs. standard-dose (70.2 Gy) RT for patients with intermediate-risk prostate cancer, Michalski indicated that the higher-dose RT resulted in fewer patients experiencing prostate-specific antigen (PSA) failures, prostate cancer progression, metastases, or initial treatment failure. The study results also show that patients in the high-dose RT arm did not live longer and experienced significantly more ≥grade 2 gastrointestinal and genitourinary side effects than patients receiving the standard dose. View the presentation and results discussion, abstract, and press release.

NRG Oncology research results also were featured during live webcast News Briefings and a Meet-the-Expert session (see sidebar below).

Featured at ASTRO

**News Briefing—Palliative Care, Quality of Life and Patient-Reported Outcomes**

**RTOG 1012**—Randomized Phase II Trial of Best Supportive Care: Manuka Honey Liquid and Manuka Honey Lozenges for Prevention of Radiation Esophagitis During Chemotherapy and Radiation Therapy for Lung Cancer

[News Briefing](#) | [Abstract](#)

**News Briefing—Advances in Lung Cancer**

**RTOG 0236**—Long-term Results of RTOG 0236: A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I Non-Small Cell Lung Cancer

[News Briefing](#) | [Abstract](#) | [Press Release](#)

**Meet-the-Expert—Technology and Biology: The Next Generation of Progress**

**RTOG 98-11**—The Significance of p16 and p53 Expression on Clinical Outcome in Patients With Anal Cancer Treated With Chemoradiotherapy: An Analysis of RTOG 98-11

**RTOG 0129**—Predictive Value of p16 Status on the Development of a Pathologic Complete Response (pCR) at Planned Neck Dissection After Cisplatin-Based Chemoradiation: A Second Analysis of RTOG 0129

**RTOG 0235**—Metabolic Tumor Volume on FDG-PET Predicts Clinical Outcomes Following Chemoradiotherapy for Locally Advanced Non-Small Cell Lung Cancer: A Secondary Analysis of ECOG-ACRIN 6668/RTOG 0235

[Meet-the-Expert](#) | [Abstracts](#)
NRG Oncology Publications Policy and Guidelines Now Available

The NRG Oncology Group Chairs recently approved the group's publications policy and guidelines, which are now available on the NRG Oncology website (see Pubs Policy 11-02-14). The document reflects the hard work and thoughtful deliberation of the NRG Oncology Publications Committee, consisting of members representing the group's diverse research community. The new policy and guidelines bring together the best attributes of the legacy groups' publication policies and guidelines.

The NRG Oncology Publications policy and guidelines apply to any publication—including abstracts, presentations, and manuscripts—that uses NRG Oncology data and/or resources. The policy lays out the process and timelines for authorship determination and publications development and submissions. “Publications are the major ‘deliverables’ of a clinical trials network, with a comprehensive publications policy serving as the fundamental document guiding timely, quality publications, as well as rewarding scholarly contributions to the work,” says Deborah W. Bruner, RN, PhD, FAAN, who is the NRG Oncology Deputy Chair for Scientific Publications and an associate director of outcomes at the Winship Cancer Institute of Emory University in Atlanta. “Because this policy is a living document, it will be reviewed and updated annually to ensure operability, integrity of publications, fair recognition of authors, and concordance with nationally recognized standards for academic publications.”

And concordance with nationally recognized standards for academic publications.

The document also describes the critical coordinating role of the NRG Oncology Publications Department, which is responsible for preparing a written timeline and submission checklist for each publication in consultation with the first author and supporting biostatistician, as well as for submitting publications to NCI, collaborators, and the designated journal.

NRG Oncology Establishes New Ancillary Projects Committee

The recent establishment of the NRG Oncology Ancillary Projects Committee provides the opportunity for investigators from a wide range of disciplines to use data collected in the conduct of NRG Oncology trials to answer important scientific questions not already specified in one of the group’s protocols. The collaboration between the applicant and NRG Oncology investigators and staff distinguishes an ancillary project from a data sharing request. Unlike the process of data sharing, which simply provides data for an investigator's independent use without the provision of NRG Oncology support, an ancillary project involves peer review and support from NRG Oncology's Statistical and Data Management Center.

The Ancillary Projects Committee is co-chaired by NRG Oncology Deputy Chair for Research Strategy Mitchell Machtay, MD, who is chair of the Department of Radiation Oncology at University Hospitals (UH) Case Western Medical Center in Cleveland; Steven Waggner, MD, who is the division chief of gynecological oncology also at UH Case Western Medical Center; and NRG Oncology Deputy Chair of Membership D. Lawrence Wickerham, MD, who is an associate professor of human oncology at the Pittsburgh Campus of Drexel University School of Medicine and the section chief of cancer genetics and prevention at Allegheny General Hospital in Pittsburgh.

Ancillary studies are a high priority for NRG Oncology as they can provide useful hypothesis-generating information of potential value to NRG Oncology’s research program and ultimately to patient care. Both NRG Oncology members and qualified nonmembers are welcome to submit ancillary project applications. “Ancillary projects are an important part of NRG Oncology’s research mission,” confirms Machtay. “These projects help us and others to develop ideas for future studies, and they can provide clues toward answering questions that may not be amenable to a prospective trial. These projects are a great opportunity for collaboration between NRG Oncology and cancer center investigators and other public and private researchers,” explains Machtay.

Investigators who wish to use data from one or more NRG Oncology studies should review the ancillary projects policy prior to completing an application form. Project applications are reviewed quarterly by the Ancillary Projects Committee. Visit Ancillary Projects Applications for more information. The policies for both ancillary and data sharing projects are located at Policies & Bylaws.

Protocol PowerPoint Presentations

PowerPoint presentations that provide protocol overview information are now available for many of the recently launched NRG Oncology trials. Site research personnel can use this resource to help facilitate discussions within their institutions about recently activated NRG Oncology trials or the prospects of opening a trial. Presentations are available currently for NRG-BR001, NRG-GI001, and NRG-LU001.