A particularly noteworthy publication from 2014 is the article entitled “Improved Survival With Bevacizumab in Advanced Cervical Cancer” by K. S. Tewari and colleagues, which was published in the New England Journal of Medicine. Through the use of a 2-by-2 factorial design, 452 patients were randomized to chemotherapy (cisplatin plus paclitaxel or topotecan) with and without bevacizumab. The data from the two chemotherapy regimens combined demonstrated that the addition of bevacizumab to chemotherapy was associated with an increase in overall survival (17.0 months vs 13.3 months), with a hazard ratio of 0.71 and a P value of 0.004. These results represent the first positive outcome of the treatment of advanced cervical cancer in a large, well-controlled trial. For his work as the study chair, Dr. Tewari was awarded the Presidents Best Paper Award at the 2014 Annual Meeting on Women’s Cancer of the Society of Gynecologic Oncology.

Having served on the Gynecologic Oncology Group’s (GOG’s) Cervix Committee since 1997, Monk became chair in 2006 and recounts the committee’s significant achievements. “The committee’s work has established the standard of care for cervical cancer internationally—both from a surgical and radiation therapy perspective—and has been instrumental in bringing two drugs for recurrent cervical cancer treatment to market,” says Monk, who emphasizes the outstanding team effort that led to these accomplishments. The GOG 179 trial (published in the Journal of Clinical Oncology in 2005) resulted in the US Food and Drug Administration (FDA) approval of the chemotherapeutic agent topotecan in 2006, and the GOG 240 trial (published in The New England Journal of Medicine in 2014) prompted an expedited FDA review and subsequent approval of the angiogenesis-inhibiting agent bevacizumab in 2014.

The GOG Cervix Committee’s work has also led to two National Cancer Institute (NCI) clinical alerts to the medical community—the most recent of which notified physicians in 1999 that adding chemotherapy to radiation therapy for the treatment of invasive cervical cancer prolonged patients’ lives.

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A NEWSPAPER FROM NRG ONCOLOGY

VOL. 2 2015

Clinical Trial Highlights

 Newly Activated Trial

NRG-GY001: A Phase II Trial of Cabozantinib (XL 184) (NSC #761968) in Women With Recurrent, Clear Cell Carcinoma of the Ovary, Fallopian Tube, or Peritoneum

Ovarian cancer is the most lethal gynecologic malignancy, with 21,980 cases and 14,270 deaths expected in the United States in 2015. Although 80% of women diagnosed with epithelial ovarian cancer—the type starts in the surface layer covering the ovary—respond to standard platinum- and taxane-based chemotherapy, most eventually develop recurrent disease that is chemotherapy-resistant and essentially incurable.

Epithelial ovarian cancer with a clear cell histology—recognized as being a particularly lethal form of the disease—is associated with a worse progression-free survival and overall survival when compared with cases of a serous histology. In a study of women with advanced epithelial ovarian cancer who were treated similarly, those with clear cell tumors had a decreased median overall survival of 24 months compared with 45 and 56 months for tumors of serous and endometrioid histologies, respectively. Clear cell ovarian cancer accounts for approximately 4% to 9.5% of ovarian tumors in the United States and for upwards of 15% to 25% of those in Japan.

Mutations in the MET gene and the overexpression of vascular endothelial growth factor (VEGF) are thought to work synergistically to promote angiogenesis, leading to the growth and spread of a number of cancers, including ovarian cancer. Preliminary research has shown that the drug cabozantinib (XL 184), which targets both MET and VEGF simultaneously, has antitumor characteristics and may be a promising treatment strategy for women with recurrent, clear cell ovarian cancer.

The phase II NRG-GY001 trial will evaluate both the efficacy and toxicity of cabozantinib in women with clear cell carcinoma of the ovary, fallopian tube, or peritoneum. The study design allows for an early determination of whether the drug demonstrates sufficient antitumor behavior to warrant full trial accrual.

Primary Objective
• To evaluate the antitumor activity of cabozantinib (XL 184) in women with persistent or recurrent clear cell ovarian cancer, based on the proportion of patients who survive progression-free for at least 6 months and the proportion who have objective tumor response (complete or partial)

Patient Population
• Patients with recurrent or progressive, clear cell ovarian cancer not based solely on the cancer antigen (CA)-125
• Patients whose primary tumor is at least 50% clear cell histomorphology or who have a histologically documented recurrence with at least 50% clear cell histomorphology

Target Accrual
Although the total accrual target for all three study phases is 31 patients, the accrual of from 27 to 34 patients is allowed due to the difficulty in accruing precise numbers of patients in a multicenter trial.
• First-stage accrual: 12 patients (range, 10–14) (If all patients have increasing disease detected on their first CT or MRI scan after the first treatment cycle, the trial will be terminated for futility.)
• Second-stage cumulative accrual: 19 patients (range, 15–22)
• Third-stage cumulative accrual: 31 patients (range, 27–34)

Schema

Patients with recurrent or persistent, clear cell ovarian cancer

Cabozantinib (XL 184) 60 mg once a day continuously, repeated in 4-week cycles until disease progression or adverse effects prohibit further therapy

“The Rare Tumor Subcommittee has developed some of the first targeted studies in gynecologic cancer. Clear cell carcinoma of the ovary is a devastating disease that is inherently resistant to chemotherapy. This study seeks to test the efficacy of exploiting specific genetic alterations found in clear cell ovarian cancer.”

JOHN H. FARLEY, MD
NRG-GY001 Principal Investigator

Please send information about special achievements of NRG Oncology members or research teams, suggestions for future articles, and regular features you would like to see in future issues of the NRG Oncology Newsletter to: info@nrgoncology.org

The NRG Oncology Newsletter is a collaboration of the Communications Committee with contributions from members and staff.

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www.nrgoncology.org
Clinical Trial Highlights (continued)

Soon-to-Activate Trial

NRG-CC001: A Randomized Phase III Trial of Memantine and Whole-Brain Radiotherapy With or Without Hippocampal Avoidance in Patients With Brain Metastases

The incidence of metastatic brain cancer is estimated to be as high as 200,000 cases per year in the United States alone. Depending upon their primary cancer type, between 10% and 30% of patients will develop brain metastases, and the incidence is on the rise due to improved cancer detection and multimodality treatments.

Whole-brain radiotherapy (WBRT) has been the mainstay of treatment for patients with intracranial metastases—especially for those with many lesions throughout the brain. It is associated with an increase in median survival of approximately 4 to 6 months. However, radiation oncologists often face the dilemma of weighing the therapeutic benefits of WBRT against the treatment’s known side effects, including a decline in memory, which can impair patients’ quality of life significantly.

Results of the RTOG 0614 trial (A Randomized, Phase III, Double-Blind, Placebo-Controlled Trial of Memantine for Prevention of Cognitive Dysfunction in Patients Receiving Whole-Brain Radiotherapy—RTOG CCOP Study) demonstrated that patients who received the drug memantine during the course of WBRT experienced significant overall delay in the onset of cognition decline. Although the addition of memantine during and after WBRT resulted in better cognitive function over time, nearly 70% of the study participants still experienced cognitive deterioration by 6 months. Given this high rate of decline, researchers continue to explore interventions to improve on the results achieved by memantine.

An intervention explored by the RTOG 0933 trial (A Phase II Trial of Hippocampal Avoidance During Whole-Brain Radiotherapy for Brain Metastases—RTOG CCOP Study) was the use of advanced radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT), to avoid radiation dose to the hippocampal region during WBRT. Exposing the hippocampus to radiation is thought to play a considerable role in memory decline. The RTOG 0933 study results provided promising evidence that the hippocampal-avoidance WBRT (HA-WBRT) technique can achieve the therapeutic benefits of WBRT while still preserving cognitive function.

The NRG-CC001 trial builds on the success of RTOG 0614 and the highly promising findings of RTOG 0933 in an effort to obtain level I evidence of the memory-preserving benefits of HA-WBRT through the conduct of a phase III trial of WBRT and memantine vs HA-WBRT and memantine in patients with brain metastases.

Primary Objective
• Determine whether the addition of HA-WBRT increases time to neurocognitive failure as measured by neurocognitive decline on a battery of tests: the Hopkins Verbal Learning Test-Revised for Total Recall, Delayed Recall, and Delayed Recognition; Controlled Oral Word Association Test; and the Trail Making Test (Parts A and B)

Target Accrual
510 patients

Patient Population
For Step 1 Registration
• Brain metastases outside a 5-mm margin around either hippocampus must be visible on contrast-enhanced MRI performed ≤21 days prior to Step 1 registration

For Step 2 Registration
• Completion of baseline neurocognitive assessments
• Pathologically proven diagnosis of solid tumor malignancy within 5 years prior to Step 2 registration

Schema

By testing the potential benefit of hippocampal avoidance (which demonstrated highly promising phase II results) in addition to memantine (which demonstrated a cognitive preservation benefit in a phase III trial), NRG-CC001 represents the upshot of almost a decade of RTOG-led investigation into the effectiveness of neuroprotective strategies to prevent radiotherapy-related cognitive toxicity.”

VINAI GONDI, M D
NRG-CC001 Co-Principal Investigator
Featured Publications

This regular newsletter feature highlights recent articles published by NRG Oncology-affiliated investigators that present the group’s scientific findings of particular importance to the care of patients with cancer. These publications represent the breadth and depth of NRG Oncology’s research endeavors.

From the Gynecologic Cancer Committee

Does Aggressive Surgery Improve Outcomes? Interaction Between Preoperative Disease Burden and Complex Surgery in Patients With Advanced-Stage Ovarian Cancer: An Analysis of GOG 182

The results of a study evaluating the effects of disease burden, complex surgery, and residual disease status on progression-free survival (PFS) and overall survival (OS) in 2,655 women with advanced epithelial ovarian cancer or primary peritoneal cancer were published online in the February 9 issue of the Journal of Clinical Oncology. All patients assessed had participated in the GOG 128 clinical trial and had either complete surgical resection or less than 1 cm of postsurgical residual disease.

Investigators found that patients with residual disease had a worse prognosis than did those in whom complete resection was achieved, with a worse PFS (15 months vs 29 months) and OS (41 months vs 77 months). Additionally, compared with patients who had either moderate or low preoperative disease burden prior to surgery, those with the highest disease burden had significantly worse PFS (15 months vs 23 or 34 months, respectively) and OS (40 months vs 71 or 86 months, respectively). This worse prognosis remained even when the researchers looked at only those patients in whom complete resection was achieved.

The authors concluded that initial disease burden remained a significant prognostic indicator despite the achievement of a complete resection. Complex surgery did not seem to affect survival when other confounding influences, particularly residual disease, were accounted for. See the abstract and read the online Exclusive Coverage review.

Nomograms Predicting Progression-Free Survival, Overall Survival, and Pelvic Recurrence in Locally Advanced Cervical Cancer Developed From an Analysis of Identifiable Prognostic Factors in Patients From NRG Oncology/Gynecologic Oncology Group Randomized Trials of Chemoradiotherapy

Investigators undertook a review of prognostic factors such as histology, race/ethnicity, performance status, and tumor size in 2,042 patients with locally advanced cervical carcinoma enrolled onto Gynecologic Oncology Group clinical trials of concurrent cisplatin-based chemotherapy and radiotherapy. The purpose was to develop nomograms to aid in estimating both individual and collective patient outcomes. A nomogram is a graph on which a number of variables are plotted so that the value of a dependent variable can be read on the appropriate line when the values of the other variables are given.1 The results of the analysis were published online in the March 2 issue of the Journal of Clinical Oncology. See abstract.


Long-Term Survival Advantage and Prognostic Factors Associated With Intraperitoneal Chemotherapy Treatment in Advanced Ovarian Cancer: A Gynecologic Oncology Group (GOG) Study

The survival benefit of intraperitoneal (IP) vs intravenous (IV) chemotherapy in women with advanced ovarian cancer extends beyond 10 years, according to the results of a retrospective analysis of GOG 114 and GOG 172 clinical trial data published online before print on March 23 in the Journal of Clinical Oncology. The authors analyzed data at a median posttreatment follow-up of 10.7 years for 876 patients with stage III ovarian cancer and no greater than 1 cm postsurgical residual disease. They report improved median survival of patients treated with IP chemotherapy (n = 440) compared with that of patients treated with IV chemotherapy (n = 436) (61.8 months vs 51.4 months, respectively). Additionally, patients treated with IP chemotherapy were 23% less likely to die from the disease, and the risk of death decreased by 12% for each cycle of IP chemotherapy completed. The authors note that these data suggest that younger patients are more likely to complete all six cycles of treatment.

“Our findings, combined with the results of previous GOG trials, continue to demonstrate the advantages of intraperitoneal chemotherapy treatment in ovarian cancer.”

DEVANSU TEWARI MD, MBA
Lead Author for the Analysis

“Our findings, combined with the results of previous GOG trials, continue to demonstrate the advantages of intraperitoneal chemotherapy treatment in ovarian cancer.”

See the abstract and read the editorial.

continued
From the Sarcoma Working Group

**Significant Reduction of Late Toxicities in Patients With Extremity Sarcoma Treated With Image-Guided Radiation Therapy to a Reduced Target Volume: Results of Radiation Therapy Oncology Group RTOG-0630 Trial**

Patients with soft tissue sarcoma of an extremity treated with preoperative image-guided radiotherapy (IGRT) experience significantly fewer long-term treatment side effects compared with a historical control group treated with preoperative, non-IGRT, according to results of the RTOG 0630 trial published online in the February 9 issue of the *Journal of Clinical Oncology*. At 2 years post treatment, 10% of patients (6/57) in the study experienced a moderate or worse side effect vs 37% of patients (27/73) in the historical control group. Specifically, treatment with IGRT was found to reduce the side effects of fibrosis (5.3% vs 31.5%), joint stiffness (3.5% vs 17.8%), and edema (5.3% vs 15.1%).

“The RTOG 0630 data demonstrate that IGRT with modern technology such as IMRT significantly improves outcomes for patients with soft tissue sarcoma and confirm that the radiotherapy parameters used in the trial should be considered appropriate for preoperative radiotherapy of extremity sarcoma.”

DIAN WANG, MD, PHD
RTOG 0630 Principal Investigator

Rush University Medical Center in Chicago, IL.

See the abstract and read the press release.

From the Lung Cancer Committee

**Pretreatment FDG-PET Metrics in Stage III Non-Small Cell Lung Cancer: ACRIN 6668/RTOG 0235**

In a secondary analysis of the ACRIN 6668/RTOG 0235 trial, investigators evaluated pretreatment FDG-PET metabolic tumor volume measures as predictors of clinical overall survival and local cancer control in patients with locally advanced non-small cell lung cancer. Two-hundred and fourteen patients were included in the overall survival and 189 in the local control analyses. Results published online in the February 16 issue of the *Journal of the National Cancer Institute* demonstrate that pretreatment metabolic tumor volume is a predictor of clinical outcomes for patients with NSCLC who are treated with chemoradiotherapy.

Read the abstract.

From the Patient Centered Outcomes Research Committee

**A Preliminary Patient-Reported Outcomes Analysis of High-Dose 3D-CRT vs IMRT for Intermediate-Risk Prostate Cancer Shows No Differences in Outcomes Between the Two Modalities**

“A preliminary analysis of patient-reported outcomes (PROs) on the high-dose arm of the RTOG 0126 clinical trial demonstrates no significant differences between intensity-modulated radiotherapy (IMRT) and 3-dimensional conformal radiotherapy (3D-CRT) in patient-reported bowel, urinary, or erectile function symptoms at any time point up to 24 months post treatment. The results were published online before print on April 2 in the journal Cancer.

This first investigation to compare PROs in similar high-dose 3D-CRT and IMRT cohorts was an important undertaking for determining whether IMRT produces greater quality-of-life improvements for patients with prostate cancer compared with 3D-CRT—especially in light of the increased cost of the additional treatment planning required for IMRT. The authors report that, although previous analyses showed that IMRT decreased radiation dose to normal tissue, this robust analysis showed no difference in patient-experienced symptoms between the two modalities.

“It seems reasonable to continue to push IMRT in the experimental setting until a threshold can be reached that maintains or improves tumor control but decreases treatment-related symptoms to the point at which patients are able to experience a noticeable improvement.”

DEBORAH W. BRUNER, RN, PHD, FAAN
Lead Author for the Analysis

“Given the high incidence of prostate cancer in the aging male population and the role that radiotherapy plays in the primary management of this disease, these results provide important insight about next steps for evaluating IMRT in the setting of intermediate-risk prostate cancer,” says Walter J. Curran, Jr, MD, an NRG Oncology Group Chair and Executive Director of the Winship Cancer Institute of Emory University in Atlanta.
NRG Oncology 2014 Outstanding Publications

Numerous manuscripts were published and abstracts were presented on behalf of NRG Oncology during the group’s first grant year. To recognize some of the exceptional research performed during 2014, the 7 disease site committee chairs each were asked to identify one manuscript and one abstract with the greatest potential impact on our understanding of a given disease state or on cancer care decision making. Following are the NRG Oncology 2014 Outstanding Publications.

Brain Tumor Committee
Abstract: Phase III study of radiation therapy (RT) with or without procarbazine, CCNU, and vincristine (PCV) in low-grade glioma: RTOG 9802 with Alliance, ECOG, and SWOG
Meeting: ASCO 2014

Manuscript: A randomized trial of bevacizumab for newly diagnosed glioblastoma

Breast Cancer Committee
Abstract: The effect on overall and disease-free survival (OS & DFS) by adding bevacizumab and/or antimitototics to standard neoadjuvant chemotherapy: NSABP Protocol B-40
Meeting: SABCS 2014

Manuscript: Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis
Publication: Lancet. 2014;384(9938):164-172

Gastrointestinal Cancer Committee
Abstract: The initial report of local control on RTOG 0436: a phase III trial evaluating the addition of cetuximab to paclitaxel, cisplatin, and radiation for patients with esophageal cancer treated without surgery
Meeting: ASTRO 2014

Manuscript: Interobserver variability in target definition for hepatocellular carcinoma with and without portal vein thrombus: Radiation Therapy Oncology Group consensus guidelines
Authors: Hong TS, Bosch WR, Krishnan S, Kim K, Mannon HJ, Shyn P, Ben-Josef E, Seong J, Haddock MG, Cheng JC, Feng MU, Stephens KL, Roberge D, Crane C, Dawson LA

Genitourinary Cancer Committee
Abstract: Initial results of a phase III randomized study of high dose 3D-CRT/IMRT vs standard dose 3D-CRT/IMRT in patients treated for localized prostate cancer (RTOG 0126)
Meeting: ASTRO 2014

Manuscript: Duration of androgen suppression before radiotherapy for localized prostate cancer: Radiation Therapy Oncology Group randomized clinical trial 9910
Publication: J Clin Oncol. Epub 2014;Dec 22

Gynecologic Cancer Committee
Abstract: Randomized phase 2 evaluation of bevacizumab vs bevacizumab-fosfotubulin in recurrent ovarian, tubal or peritoneal carcinoma: an NRG Oncology/Gynecologic Oncology Group study
Meeting: IGCS 2014
Authors: Monk BJ, Mannel RS, DiSilvestro P, Mutch D, Tewari K, Pajon E, Martin LP, Schilder R

Manuscript: Temsirolimus with or without megestrol acetate and tamoxifen for endometrial cancer: a Gynecologic Oncology Group study
Publication: Gyencol Oncol. 2014;132:585-592

continued
Outstanding Publication Awards (continued)

Head & Neck Cancer Committee

Abstract: The KRAS variant and cetuximab response in RTOG 0522

Meeting: ASCO 2014


Manuscript: Postoperative chemoradiation therapy and cetuximab for high-risk squamous cell carcinoma of the head and neck: Radiation Therapy Oncology Group RTOG-0234

Publication: J Clin Oncol. 2014;32:2486-2495

Authors: Harari PM, Harris J, Kies MS, Myers JN, Gillison ML, Foote RL, Machtay M, Rotman, M, Khuntia D, Straube W, Zhang Q, Ang K

Lung Cancer Committee

Abstract: 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

Meeting: ASTRO 2014


Manuscript: EGFR expression and survival in patients given cetuximab and chemoradiation for stage III non-small cell lung cancer: a secondary analysis of RTOG 0324

Publication: Radiother Oncol. 2014;112:30-36


Program Updates

Are You “In the Know” About NRG Oncology?

Since the group’s official beginning on March 1, 2014, NRG Oncology’s communications to its research community have evolved in an effort to provide timely and concise information about a broad range of topics pertaining to the group’s research program. “Our goal is to provide site research teams with easy access to the information they need to carry out NRG Oncology studies and to make all aware of the group’s major achievements,” says Carmen Allegra, MD, Deputy Group Chair for Communications.

The NRG Oncology website serves as the all-inclusive resource for information about the group’s activities. As programs have been developed and policies have been finalized, new content and materials have been posted to the website at www.nrgoncology.org. Most recently, in the website’s new Scientific Program section, the NRG Oncology executive team, committee chairs, and committee co-chairs have been introduced, with a link to each investigator’s institutional profile also provided. Additionally, information about NRG Oncology’s National Cancer Institute (NCI) Community Oncology Research Program (NCORP) Research Base has been posted to include an overview of the NCORP committees, program resources, and a listing of NCORP-sponsored trials.

In August 2014, NRG Oncology launched the Weekly Broadcast communication e-mailed to affiliated researchers every Monday. Considerable planning occurred prior to initiating this weekly update to thoughtfully meld the best practices of the legacy groups in keeping members up-to-date about regulatory and protocol updates, membership information, upcoming national meetings, and other news. (See the Weekly Broadcast announcement for information about how to receive these updates.) The Weekly Broadcast communications are archived on the group website at Weekly Broadcast archives. Additionally, occasional Special Announcement e-mails are distributed to inform research teams about especially time-sensitive issues or events, and Research Results e-mail communications bring to members’ attentions key research findings with a direct effect on patient care.

Another communications vehicle is the NRG Oncology Newsletter, which is distributed approximately six times annually and regularly features messages from the group chairs, committee leadership profiles, and new program information, among other updates and news items. “We strive to strike a balance of providing information of interest without overwhelming researchers with too many e-mails, and we encourage our audiences to let us know if we have achieved the right balance,” says Allegra.
**Spotlight: NRG Oncology Cervix/Vulva Cancer Subcommittee (continued from page 1)**

“This NCI alert resonated worldwide and, because the results were so dramatic, changed the standard of care. Now, virtually every patient with cervical cancer who receives radiation therapy also receives chemotherapy,” says Monk.

Despite the development of far fewer large cervical cancer trials expected to result from the downsizing of the NCI cooperative group network, Monk points out, “The NRG Oncology Cervix/Vulva Cancer Subcommittee is engaged in 7 trials—3 of which are phase III—that are currently accruing patients. This high level of activity speaks to the tremendous subcommittee teamwork and volunteerism involved.” Monk also cites the valuable clinical and organizational expertise of the subcommittee’s co-chair, Wui-Jin Koh, MD, as instrumental to its productivity. Koh is a professor of radiation oncology at the University of Washington and the medical director for radiation oncology for Seattle Cancer Care Alliance.

A relatively new subcommittee focus is the activity of immunotherapeutic agents, which Monk deems as the next frontier in cancer therapeutics. The phase II GOG 265 trial is evaluating the vaccine ADXS11-001 for treating patients with persistent or recurrent cervical cancer. Soon to activate is another phase II trial evaluating an anti–PD-1 agent for a similar patient population.

Another aspect of cervical cancer research of great interest to Monk is the need for special population outreach. “Because cervical cancer is essentially 100% preventable with vaccination, Papanicolaou (or Pap) testing, and testing for cervical HPV, women who are diagnosed with cervical cancer have been failed by the health care system. These women tend to be ethnically diverse, from a lower socioeconomic status, and/or living in rural communities. They deserve our help, our clinical trials, and more of our focus,” says Monk.