Message From Our NRG Oncology Group Chairs

Norman Wolmark, MD

March 1, 2015 was the first birthday of NRG Oncology, and there was lots to celebrate. Total NRG Oncology accrual to all National Clinical Trials Network (NCTN) studies during the first 12 months was 5,707—the largest accrual total among the adult research groups in the NCTN. NRG Oncology members include 29 of the 30 NCI-funded Lead Academic Performance Sites (LAPS), and number 30 is applying for membership. LAPS accounted for 30% of the total NRG Oncology participant accrual in year 1. NRG Oncology is a research base for the National Community Oncology Research Program (NCORP), and almost all of the NCORP sites or Minority/Underserved NCORP sites are NRG Oncology members. Those NCORP sites contributed 20% of the accrual to NRG Oncology treatment trials.

NRG Oncology Canadian members enrolled about 7% of the patients accrued during year 1. I grew up in Canada, and I am a graduate of McGill University for both my undergraduate and medical school degrees. I have a strong commitment to maintain and expand the scope of NRG Oncology studies in Canada.

The remaining clinical trial accrual came from our other Main Members in the United States, as well as our International Members. During the second year of NRG Oncology, we hope to continue to provide a menu of scientifically important and clinically interesting studies (5 have opened since March 1) that will allow our accrual figures to continue to improve.

Like any developing infant, NRG Oncology will continue to have growing pains. Change is always a challenging process, but it will be vital for the long-term success of NRG Oncology. The three Group Chairs and the entire senior leadership team are always willing to listen to any and all suggestions to improve our research group.

Thank you, and I look forward to seeing you at our next NRG Oncology semiannual meeting in Denver this July.

NRG Oncology has leveraged the research group’s prominence in the field of radiation oncology to establish the Center for Innovation in Radiation Oncology (CIRO), a multidisciplinary program to promote innovative radiotherapy (RT) research and foster intergroup collaboration within the National Clinical Trials Network (NCTN). CIRO was established in response to the National Cancer Institute’s Funding Opportunity Announcement calling for a resource to support high-quality RT in all trials carried out by the NCTN research groups. "CIRO helps fulfill the NCI’s mission to have its clinical trial portfolio function as a network. CIRO builds on our expertise in radiation oncology to serve the entire NCTN," says Walter J. Curran, Jr, MD, an NRG Oncology Group Chairman and Executive Director of the Winship Cancer Institute of Emory University in Atlanta. CIRO’s program comprises the NRG Oncology Radiation Oncology Committee, along with its Medical Physics Subcommittee and soon-to-be-established Diagnostic Imaging Subcommittee.

"The formation of NRG Oncology brought together expanded RT expertise under CIRO," says Radiation Oncology Committee Chair Jeff M. Michalski, MD, MBA, FASTRO, and the Carlos A. Perez Distinguished Professor of radiation oncology at Washington University in St. Louis, who emphasizes the significant contribution of the committee’s co-chairs, Ivy A. Petersen, MD, and Frank A. Vicini, MD. “They are great leaders in the field, and I’m delighted to work with them.” Both radiation oncology researchers, Peterson specializes in gynecologic cancers at Mayo Clinic in Rochester, Minnesota and Vicini focuses on...
New Clinical Trials

NRG-BR003: A Randomized Phase III Trial of Adjuvant Therapy Comparing Doxorubicin Plus Cyclophosphamide Followed by Weekly Paclitaxel With or Without Carboplatin in Node-Positive or High-Risk, Node-Negative, Triple-Negative Invasive Breast Cancer

Triple-negative breast cancer (TNBC), which accounts for approximately 15% to 20% of all newly diagnosed breast cancer cases, is characterized by tumors that test negative for the estrogen receptor (ER), progesterone receptor (PgR), and HER-2/neu receptor molecular tumor markers. Although targeted therapies are available for patients whose breast cancer tests positive for one of these molecular tumor markers, no molecular targets exist currently to guide the treatment of TNBC. Patients with TNBC have an increased likelihood of distant recurrence and of death compared with those with other types of breast cancer, with the highest rates of recurrence at 1 to 4 years after diagnosis.1

The NRG-BR003 trial was developed to address the need to improve the outcomes of patients with early high-risk TNBC. Specifically, the phase III randomized trial will assess the value of adding carboplatin to the adjuvant chemotherapy regimen of dose-dense doxorubicin plus cyclophosphamide followed by weekly paclitaxel compared with the adjuvant chemotherapy alone in patients with operable node-positive or high-risk, node-negative TNBC.

Prior study results suggest that TNBC has a high sensitivity to DNA-damaging agents, such as carboplatin, that bind to the DNA in a cell’s nucleus and form DNA crosslinks that lead to cell death. No clinical trials are being conducted currently in the adjuvant setting to assess the value of adding carboplatin to standard chemotherapy. The NRG-BR003 trial has the potential to change current medical practice if the addition of carboplatin to chemotherapy leads to results that are superior to those from chemotherapy alone in patients with high-risk TNBC.

Primary Objective
To determine whether the addition of carboplatin to an adjuvant chemotherapy regimen of doxorubicin/cyclophosphamide followed by paclitaxel will improve invasive disease-free survival compared with doxorubicin/cyclophosphamide followed by paclitaxel alone when administered to patients with operable node-positive or high-risk, node-negative TNBC

Secondary Objectives (Summary)
• To determine whether the addition of carboplatin to an adjuvant chemotherapy regimen of doxorubicin/cyclophosphamide followed by paclitaxel will improve overall survival, breast cancer-free survival, the recurrence-free interval, and the distant recurrence-free interval

• To compare the toxicities of the adjuvant chemotherapy regimens

Target Accrual
990 patients

Patient Population
Patients with resected node-positive or high-risk, node-negative HER-2/neu-negative, ER-negative, and PgR-negative invasive breast cancer

Schema

Patients With Resected Node-Positive or High-Risk, Node-Negative

<table>
<thead>
<tr>
<th>STRATIFICATION</th>
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<tbody>
<tr>
<td>Number of positive nodes: 0, 1–3, 4–9, 10+</td>
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<tr>
<td>BRCA mutation status: positive, negative or unknown</td>
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<table>
<thead>
<tr>
<th>RANDOMIZATION</th>
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<tbody>
<tr>
<td>Arm 1</td>
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<tr>
<td>AC followed by weekly paclitaxel</td>
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</table>

AC = doxorubicin (A) + cyclophosphamide (C)

NRG Oncology Trials Evaluate Immunotherapeutic Agents

Three new NRG Oncology trials are exploring promising immunology treatment strategies for patients with lethal cancers for which new therapeutic options are needed greatly. The trials are assessing nivolumab alone or in combination with ipilimumab—both targeted monoclonal antibody agents that act on “immune checkpoint” proteins that control the immune system’s ability to eliminate cancer cells. Nivolumab targets the programmed cell death protein 1 (PD-1) located on the...
New Clinical Trials (continued)

A Phase I Study of Ipilimumab, Nivolumab, and the Combination in Patients With Newly Diagnosed Glioblastoma

Background
Despite advances in surgery, radiation therapy, and chemotherapy, patients with newly diagnosed glioblastoma have a poor prognosis, with a median survival of 14 to 16 months. This underscores the urgent need for better therapeutic options for this patient population. Although immunotherapy historically has shown efficacy in the treatment of other cancers, such as melanoma, prostate, and renal cell cancer, these approaches have not been successful in the treatment of primary brain tumors. Recent investigations have demonstrated that the glioblastoma tumor produces factors that cause an immunosuppressive state, both in the brain as well as systemically, thereby inhibiting a robust endogenous response to the brain tumor. Extensive laboratory studies have uncovered many of the mechanisms of this immunosuppression. In particular, the activation of T regulatory (Treg) cells and anergy secondary to effector T-cell exhaustion are major contributors to the cancer-associated immunosuppressed state. However, treatments that block two of the main modulators of immunosuppression, CTLA-4 and PD-1, have proven effective recently in the treatment of metastatic melanoma and other cancers, such as non-small cell lung cancer. These treatment strategies may be effective in the treatment of malignant primary brain tumors, which exhibit prominent Treg effects.

Evaluating the safety of specific immunotherapeutic agents for the treatment of glioblastoma, especially in combination with standard-of-care therapies, is an important first step in the process of investigating potential new treatment options. The phase I NRG-BN002 clinical trial is assessing the maximum safe dose of the immunotherapeutic drugs ipilimumab and nivolumab administered alone and in combination, with standard temozolomide maintenance chemotherapy.

The NRG-BN002 trial is expected to open as early as June and will enroll patients at a limited network of NRG Oncology research sites that treat a large number of patients with glioblastoma. After undergoing surgery, all patients receive standard temozolomide chemotherapy and radiotherapy. At 4 to 6 weeks after completing this primary treatment, patients enter the study and are randomized to protocol treatment with maintenance temozolomide and ipilimumab (Cohort 1) or nivolumab (Cohort 2) to determine the maximum safe dose of both drugs. If the side effects experienced by Cohort 1 and Cohort 2 are found to be acceptable, patient enrollment for the evaluation of the combination of ipilimumab and nivolumab with adjuvant temozolomide (Cohort 3) will begin. However, if either ipilimumab or nivolumab is determined to be too toxic at the single-agent dose level, the combination will not be tested.

Primary Objective
To determine the maximum safe dose of single-agent treatment with ipilimumab and nivolumab, alone and in combination, when given with temozolomide during maintenance treatment for newly diagnosed glioblastoma.

Patient Population
• Patients with a histopathologically proven diagnosis of glioblastoma or gliosarcoma prior to registration by pathology report
• Patients who have undergone a gross total or near gross total resection of a tumor that is unifocal and confined to the supratentorial compartment

Target Accrual
42 patients

Schema
Please see the NRG-BN002 protocol to review the extensive schema.

NRG by the Numbers
The second grant year, starting March 1, 2015, is off to a strong start for NRG Oncology, with 862 participants accrued into the group’s treatment trials through May 31. The top ten accrual trials for this time period are below.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients Enrolled</th>
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<tbody>
<tr>
<td>RTOG 0924</td>
<td>92</td>
</tr>
<tr>
<td>GOG 0286B</td>
<td>68</td>
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<tr>
<td>NSABP B-52</td>
<td>65</td>
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<tr>
<td>NRG CC002</td>
<td>52</td>
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<td>RTOG 0815</td>
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<td>RTOG 1203</td>
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<tr>
<td>RTOG 1216</td>
<td>32</td>
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</tbody>
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New Clinical Trials (continued)

NRG-GY003: A Phase II Randomized Trial of Nivolumab With or Without Ipilimumab in Patients With Persistent or Recurrent Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer

Background
Epithelial ovarian and related cancers account for the majority of gynecologic cancer deaths. Despite receiving front-line therapy including surgical resection and combination platinum-taxane chemotherapy, the vast majority of patients experience cancer recurrence and ultimately die from the disease. The NRG-GY003 trial also is assessing the two immunotherapeutic agents nivolumab and ipilimumab for their potential to improve the outcome of patients with persistent or recurrent epithelial cancers of the ovary, peritoneum, or fallopian tube. Results of a phase I trial of nivolumab in women with platinum-resistant ovarian cancer provide preliminary evidence of the single agent’s activity in patients with highly pretreated, platinum-resistant ovarian cancer. Additionally, laboratory and clinical research results suggest that concurrent administration of nivolumab and ipilimumab can act complementarily to provide significant clinical activity in epithelial ovarian cancer and related malignancies.

Another important trial component is the assessment of potential population-specific safety issues and effective supportive care measures related to adverse effects unique to these agents. The trial’s translational research objectives seek to determine whether cellular and molecular laboratory parameters in pretreatment tissue and peripheral blood specimens predict overall survival, tumor response by modified Response Evaluation Criteria in Solid Tumors (RECIST) (Version 1.1), and progression-free survival.

To be eligible for the trial, a patient’s cancer must have progressed in less than 12 months after completion of the last platinum-based chemotherapy. Upon meeting all the eligibility requirements, study participants are randomized to receive nivolumab or nivolumab plus ipilimumab, followed by maintenance therapy with nivolumab.

Primary Objectives
- To estimate the proportion of patients who have objective tumor response (complete or partial) by modified RECIST 1.1 in patients with persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancers treated with nivolumab or the combination of nivolumab and ipilimumab
- To assess the objective response rate (ORR) in patients treated with nivolumab compared with that in patients treated with the combination of nivolumab and ipilimumab

Patient Population
- Patients with recurrent or persistent epithelial ovarian, fallopian tube, or primary peritoneal cancer with documented disease progression
- Patients with measurable disease and at least one target lesion by which to assess response by RECIST 1.1

Target Accrual
- First stage: 48 patients (24 patients within each arm)
- Second stage (if warranted): 48 patients (24 patients within each arm)

Schema

NRG-GY002: A Phase II Evaluation of Nivolumab, a Fully Human Antibody Against PD-1, in the Treatment of Persistent or Recurrent Cervical Cancer

Background
Patients with cervical cancer that has recurred or metastasized who have been treated subsequently with paclitaxel and cisplatin, or this regimen plus bevacizumab, face limited therapeutic options should their cancer progress. Recent studies across a range of cancer types have reported encouraging results for the use of agents that block either the PD-1 protein (located on the surface of T cells) or the PD-1 ligand (PD-L1) protein (located on the surface of cancer cells). The NRG-GY002 clinical trial will assess both the antitumor activity of nivolumab and the drug’s toxicity in patients with persistent or recurrent cervical cancer who have undergone one prior systemic chemotherapeutic regimen for the management of persistent, recurrent, or metastatic disease.

"It’s clear today that immune treatments can help patients with bladder, genitourinary, and head and neck cancers as well as melanoma and lung cancer. Anti-PD-1 antibodies have changed the lives of many patients, and it’s exciting to see that nivolumab will now be available within NRG Oncology clinical trials for patients with cervical cancer.”

ALESSANDRO D. SANTIN, MD
NRG-GY002 Principal Investigator

Human papillomavirus (HPV) DNA is detected in more than 99% of cervical cancer cases. Although a variety of factors may potentially predict clinical response to nivolumab in
New Clinical Trials (continued)

patients with cervical cancer, limited information is available regarding PD-1 and PD-L1 expression on cervical HPV-infected tumor cells and T cells infiltrating cervical cancers. Accordingly, this study will evaluate systematically PD-1 and PD-L1 expression in tumor-infiltrating lymphocytes (TILs) and cervical cancer cells.

Primary Objectives

• To assess the antitumor activity (proportion of objective response by RECIST 1.1 criteria) of nivolumab with objective tumor response in patients with persistent, recurrent, or metastatic carcinoma of the cervix

• To determine the nature and degree of toxicity of nivolumab as assessed by Common Terminology Criteria for Adverse Events (CTCAE) in patients with persistent, recurrent, or metastatic carcinoma of the cervix

Patient Population

• Patients with persistent, recurrent, or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix with documented disease progression (disease not amendable to curative therapy)

• Patients who have undergone one prior systemic chemotherapeutic regimen for the management of persistent, recurrent, or metastatic disease

Target Accrual

• First stage: 12 patients

• Second stage (if warranted): 13 patients

Schema

<table>
<thead>
<tr>
<th>Patients With Persistent, Recurrent, or Metastatic Cervical Cancer</th>
</tr>
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<tbody>
<tr>
<td>Nivolumab</td>
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<tr>
<td>3 mg/kg IV every 2 weeks for 4 doses, followed by an additional 42 doses 3 mg/kg IV every 2 weeks, for a maximum of 46 doses over 92 weeks until disease progression or adverse effects prohibit therapy, whichever comes first</td>
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NRG NCORP Program Updates

New NRG NCORP Trial Activates

NRG-CC003: Randomized Phase II/III Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance for Small Cell Lung Cancer

Background

Approximately 50% to 60% of patients diagnosed with small cell lung cancer (SCLC) develop brain metastases some time during the course of their disease. The burden of brain metastases negatively affects patients’ quality of life and shortens their survival.

Clinical trials evaluating prophylactic cranial irradiation (PCI) in patients with SCLC have shown a reduction in the incidence of brain metastases and lengthened survival with the administration of PCI. However, in spite of this evidence, a recent study demonstrated that 40% of patients with limited-stage SCLC do not receive PCI due to both patient and physician concerns about the effect of PCI on cognition.1

“NRG-CC003 builds upon the highly promising results of RTOG 0933 and seeks to test whether conformal avoidance of the hippocampus during PCI using IMRT can provide the therapeutic benefit of PCI for the treatment of small cell lung cancer, but without the cognitive toxicities that can often impact quality of life negatively.”

VINAI GONDI, MD
NRG-CC003 Co-Principal Investigator

Preclinical and clinical studies suggest that radiation-induced damage to the hippocampus plays a considerable role in patients’ cognitive decline. The RTOG 0933 trial (A Phase II Trial of Hippocampal Avoidance During WBRT for Brain Metastases—RTOG CCOP Study) explored a novel, highly conformal approach to delivering whole brain radiotherapy (WBRT) using intensity-modulated radiotherapy (IMRT) to avoid radiation dose to the hippocampal region. The RTOG 0933 study results provide promising evidence that the hippocampal-avoidance WBRT (HA-WBRT) technique can achieve therapeutic benefits while still preserving cognitive function.

The NRG Oncology trial (NRG-CC003) will test further the hypothesis that hippocampal avoidance may prevent radiotherapy-induced cognitive decline, but within the context of PCI for SCLC. The same IMRT techniques used in the RTOG 0933 trial will be used in this trial to conformally avoid the hippocampal region during PCI. The investigators hypothesize that hippocampal-avoidance PCI (HA-PCI) may delay or reduce the onset, frequency, and/or severity of cognitive decline (as measured with clinical cognitive tools) in patients with SCLC.

Primary Objectives

• Randomized Phase II Component (Noninferiority): Determine whether HA-PCI has a similar 12-month intracranial relapse rate compared with PCI for patients with SCLC

• Phase III Component: Determine whether HA-PCI reduces the likelihood of 6-month deterioration from baseline in Hopkins Verbal Learning Test-Revised (HVLT-R) delayed recall compared with PCI for patients with SCLC

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VINAI GONDI, MD
NRG-CC003 Co-Principal Investigator

Preclinical and clinical studies suggest that radiation-induced damage to the hippocampus plays a considerable role in patients’ cognitive decline. The RTOG 0933 trial (A Phase II
NRG NCORP Program Updates (continued)

Patient Population
Patients with SCLC who have no radiographic evidence of central nervous system (CNS) metastases

Target Accrual
304 patients

Schema

Histologic Proof or Unequivocal Cytologic Proof of SCLC

**STEP 1 REGISTRATION**

**Stratification**

Cancer stage: Concurrent memantine: Age:
1. Limited 1. Yes 1. <60
2. Extensive 2. No 2. ≥60

**STEP 2 REGISTRATION**

Baseline neurocognitive assessment required

**RANDOMIZATION**

Arm 1
PCI alone using 3D-CRT
(25 Gy in 10 fractions)

Arm 2
HA-PCI using IMRT
(25 Gy in 10 fractions)

3D-CRT = three-dimensional conformal radiation therapy.


NRG NCORP Trial in Focus: GOG 0237
NRG NCORP Trial Investigates Promising Biomarkers to Guide Treatment Decision Making for Women Diagnosed With Cervical Atypical Glandular Cells

Several changes in a recent GOG 0237 protocol amendment are expected to boost patient enrollment into this NRG NCORP trial, which examines biomarkers to determine which subset of biomarkers are optimal for detecting all precancerous cervical lesions in patients with atypical glandular cells (AGC) (Click on protocol summary for information about protocol biomarkers). Specifically, prior to the recent amendment, all patients with an AGC diagnosis had to agree to undergo a cone biopsy procedure as part of study participation regardless of tumor human papillomavirus (HPV) status. However, in alignment with current cervical cancer screening guidelines, the amended protocol now allows North American study participants whose cytology is found to be HPV-negative to discontinue study participation (with documentation of a negative HPV test result submitted to the NRG Oncology Statistical and Data Management Center).

Another protocol change intended to help accrual across all locations (the study also is being conducted in Japan and Korea, with results from each population to be analyzed separately) expanded the eligibility criteria to include enrollment of patients diagnosed with adenocarcinoma in situ of the cervix.

“Clinicians are faced with the dilemma of how aggressively to treat patients who present with AGC. The results of this trial have the potential to validate biomarkers that can be used to distinguish relevant premalignant and malignant cervical lesions from normal and benign tissues,” says the trial’s principal investigator, Shu-Yuan Liao, MD. Liao explains that the GOG 0237 trial builds upon information gained from the predecessor GOG 0171 trial, which found that testing for carbonic anhydrase (CA) IX (CA-IX) in combination with HPV was important to identify which patients diagnosed with AGC had significant lesions; however, the specificity of the combined biomarkers was only 70% in the North American population and 44% in the Japanese population.

Additionally, the GOG 0171 data show the existence of a unique type of cervical cancer in the Japanese population that is HPV-negative and CA-IX-positive, and the GOG 0237 data are expected to provide additional insight about this finding, along with other important information that will contribute to determining the optimal cervical cancer screening strategies regardless of ethnic origin.

A target number of true-positive cases with complete data has been established for each geographic location: 222 cases from North America, 100 cases from Japan, and 100 cases from Korea. To date, the Japanese sites have enrolled more than 300 patients and are expected to reach their accrual goal very soon. Korea, having opened the study relatively recently, has enrolled more than 70 patients, and North American sites have enrolled more than 210 patients. An additional 300 or more patients need to be enrolled in North America to reach the target number of 222 true-positive cases—so, there is still an opportunity for new sites to open the trial and enroll patients.

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SHU-YUAN LIAO, MD
GOG 0237 Principal Investigator

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“This trial is very straightforward to carry out,” says Liao. “However, it is important to develop a system for identifying potential study participants, especially because most patients are under the care of a primary care physician or gynecologist when they are diagnosed with AGC.” Liao recommends strongly that each GOG 0237 site research team establish frequent communication with the primary treating physicians.

continued
NRG NCORP Program Updates (continued)

Below are examples of glandular cells from a Pap stain that appear morphologically similar; however, the left image shows reactive atypia cells that are benign, and the right image shows an adenocarcinoma in situ. Additional biomarkers are needed to distinguish relevant premalignant and malignant cervical lesions from normal and benign tissues.

so that the physicians remember to bring up the prospect of trial participation with eligible patients. Another enrollment strategy that Liao suggests is for the site to keep in regular contact with the coordinators of the gynecologic clinic.

The GOG 0237 trial results have the potential to have a significant impact in determining the best care for patients diagnosed with ACG.

Preventing Adenomas of the Colon With Eflornithine and Sulindac (PACES S0820)

More than 1 million colorectal cancer survivors live in the United States today, and the number continues to grow. After completing treatment for colorectal cancer and being cancer-free, these patients remain at a higher risk for developing precancerous adenomas or second primary colorectal cancers than the general population.

The PACES (SWOG S0820) study seeks to learn whether two drugs that have shown early promise can lower the risk of high-risk adenomas or second primary colorectal cancers significantly for survivors of colon and rectal cancer.

PACES is enrolling about 1500 patients who have recently completed surgery (with or without radiation therapy or chemotherapy) for stage 0–III colon or rectal cancer. At approximately 1 year (6–15 months) after tumor resection participants are randomized to receive eflornithine 500 mg/day alone, sulindac 150 mg/day alone, eflornithine 500 mg/day plus sulindac 150 mg/day, or 2 placebos daily for 3 years. Participants then undergo a colonoscopy (ie, at study year 3, which corresponds to postoperative year 4), continue to be followed annually for 5 years following the termination of drug intervention, and undergo a follow-up colonoscopy 8 years after enrolling in the study.

Eflornithine (also known as difluoromethylornithine [DFMO]) has been used intravenously to treat trypanosomiasis (sometimes called “sleeping sickness”) and as a skin cream to reduce unwanted hair growth.

Sulindac is a nonsteroidal anti-inflammatory drug (NSAID) used to treat arthritis pain. It has been shown to reduce the number of colon polyps in patients with familial adenomatous polyposis, an inherited condition in which the patient develops hundreds or even thousands of such polyps.

“We can do more to prevent cancers by targeting groups at greater risk,” states Study Chair Jason A. Zell, DO, MPH. “Colorectal cancer survivors in particular stand to benefit from further risk reduction strategies.”

“PACES is a clinically interesting and scientifically sound trial,” says D. Lawrence Wickerham, MD, Deputy Group Chair of the NRG Oncology Membership Committee. “NRG Oncology is pleased to support the study and make it available to all NRG sites. Members can obtain NRG Oncology accrual credit at the time of patient entry.”

More than 500 institutions in the United States are participating in the PACES study. Interested physicians can click here to find a nearby participating institution and obtain more information online at www.swog.org or at www.ctsu.org, or by contacting SWOG at (210) 614-8808 or at protocols@swog.org. The trial is funded by the National Cancer Institute, Division of Cancer Prevention.
From the Genitourinary Cancer Committee
Long-term follow-up results of the RTOG 9902 trial reported recently in the International Journal of Radiation Oncology • Biology • Physics showed that the addition of adjuvant chemotherapy (paclitaxel, estramustine, and oral etoposide [TEE]) to treatment with long-term androgen suppression (AS) therapy plus radiotherapy (RT) did not provide a survival benefit in patients with high-risk, clinically localized prostate cancer. Early closure of the trial due to excess toxicity noted in the chemotherapy arm resulted in its accrual goal not being met (397 of the target 1440 study participants were enrolled).

Although the findings were negative, the authors report that the trial provided valuable data about the natural history of high-risk prostate cancer (median follow-up was 9.2 years) and demonstrated that patients with nonmetastatic, high-risk disease could be enrolled on a phase III trial in which they would be randomized to treatment with chemotherapy versus no chemotherapy.

According to Seth Rosenthal, MD, FACR, the paper’s lead author, “significantly, the RTOG 9902 trial results provided a basis for the RTOG 0521 successor trial led by Howard Sandler, MD, who presented that trial’s initial results at ASCO 2015.” Rosenthal notes that the results of the follow-on RTOG 0521 trial, which accrued 612 patients, showed improved overall survival for patients treated with the combination of long-term AS therapy and RT combined with docetaxel compared with those treated with long-term AS and RT alone (see ASCO release).

“The RTOG 9902 trial demonstrated the ability of NRG Oncology researchers to pioneer the use of multimodality treatment in new disease sites and to accrue successfully patients with localized disease to randomized, phase III trials in the cooperative group setting,” says Walter J. Curran, Jr, MD, an NRG Oncology Group Chairman and Executive Director of the Winship Cancer Institute of Emory University in Atlanta.

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

Outstanding NRG Oncology Member Institutions to Be Announced
Research sites that turned in an outstanding performance during the group’s first grant year (March 1, 2014 through February 28, 2015) will be recognized during the NRG Oncology General Session taking place on Saturday, July 18 from 1:00 PM – 2:30 PM.

Research teams at these sites demonstrated the ability to enroll patients into NRG Oncology and NRG NCORP trials and to maintain excellent data quality. After the meeting, visit the NRG Oncology website to view the list of these top-performing institutions at NRG Oncology Outstanding Site Participation Awards.
Semiannual Meeting Highlights

The NRG Oncology Semiannual Meeting, to take place July 16–July 19 in Denver, Colorado, provides attendees the opportunity to gain a better understanding of NRG Oncology’s science and operations, learn from cancer research experts, and exchange information with colleagues from around the country. Each meeting session has much to offer; following are just a few of the highlights.

NRG Oncology Protocol Kick-Off Meetings and Workshops

NRG-CC003 Kick-Off Presentation
Friday, July 17, 2015; 8:00 AM–9:00 AM

Be among the first to learn about the NRG-CC003 trial (see page 5) at the kick-off meeting, during which trial leadership will present the background and objectives of the phase II/III clinical trial evaluating whether a hippocampal avoidance technique used during prophylactic cranial irradiation in patients with small cell lung cancer delays or reduces the onset, frequency, or severity of the patients’ cognitive decline. Additionally, specifics about how to perform the hippocampal avoidance technique will be detailed, along with other important considerations for conducting the trial.

NSABP B-51/RTOG 1304 Workshop: Be Part of the Debate!
Friday, July 17, 2015; 3:00 PM–4:00 PM

Why is it important for your site to accrue patients to the NSABP B-51/RTOG 1304 trial? With the increasing use of neoadjuvant chemotherapy, a commonly encountered clinical scenario involves patients who present with breast cancer and pathologically involved axillary nodes, receive neoadjuvant chemotherapy, and are found to have pathologically node-negative disease at the time of definitive surgery. An active debate exists about the appropriate use (and extent) of locoregional radiotherapy (RT) after mastectomy or breast-conserving surgery for such patients. On one hand, because these patients present with known positive axillary nodes, they are at high risk for locoregional recurrence (LRR) and should receive RT to the chest wall and regional nodal basins (after mastectomy) or to the regional nodal basins in addition to breast RT (after lumpectomy). On the other hand, sterilization of involved axillary nodes by neoadjuvant chemotherapy lowers the risk of LRR, making the need for RT to the chest wall and regional nodal basins after mastectomy and to the regional nodal basins (after lumpectomy) questionable.

Come to the NSABP B-51/RTOG 1304 Workshop to learn more about an RT trial that may end the debate and establish a new standard of care. A member of the protocol leadership will discuss trial updates, as well as provide tips to help you identify potential patients at your site. This is an exciting trial, and NRG Oncology wants your site to be part of it. Don’t miss out on this opportunity to learn more about this exciting research.

NRG Protocols NSABP B-52, NSABP B-55, and NRG-BR003 Workshop
Saturday, July 18, 2015; 12 PM–1:00 PM

Consider attending the NSABP B-52, NSABP B-55, and NRG-BR003 Workshop. Vicente Valero, MD, will discuss NRG-BR003, an adjuvant therapy trial for men and women with node-positive or high-risk, node-negative, triple-negative invasive breast cancer. This trial was activated on June 26, 2015. Priya Rastogi, MD, will discuss the NSABP B-55 trial, which is open currently for accrual. This trial will assess the efficacy and safety of olaparib as adjuvant treatment in men and women with germline BRCA1/2 mutations and high-risk HER2-negative breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy. Additionally, Dr. Rastogi will provide an update on the NSABP B-52 trial. This trial will evaluate the pathologic complete response rates in patients with hormone receptor-positive, HER2-positive, large operable and locally advanced breast cancer treated with neoadjuvant therapy with or without estrogen deprivation.

Center for Innovative Radiation Oncology (CIRO) Workshops

The Radiation Oncology Workshop
Friday, July 17, 2015; 1:30 PM–3:30 PM

Medical Physics Subcommittee Workshop
Friday, July 17, 2015; 3:30 PM–6:00 PM

Do you want to learn about new and novel technologies in the field of radiation oncology? If so, plan to attend the CIRO workshops to hear presentations about exciting developments in the field and how CIRO is supporting their implementation in NCTN clinical trials. All are welcome!

Follow NRG Oncology in Denver on Twitter!

We will be tweeting during the NRG Oncology Semiannual Meeting in Denver on Twitter. If you are already on Twitter, use the hashtag #NRGMtg15 in your tweets so researchers can follow your posts about the meeting. If you are not part of Twitter, now is a great time to get started. Get connected with your colleagues who are tweeting about the meeting and other important medical news. And don’t forget to follow us @NRGonc.
CIRO (continued from page 1)

breast cancer at 21st Century Oncology of Michigan in Farmington Hills.

Center for Innovation in Radiation Oncology Aims

1. Promote innovative RT research within the entire NCTN
   - Accelerate the testing of new radiation oncology innovations in NCTN clinical trials in all research groups
   - Facilitate the application of innovations across all appropriate protocols
2. Foster intergroup collaboration and protocol harmonization in terms of inclusion and description of RT techniques and delivery devices
   - Reduce timelines for the development of new protocols
   - Improve the clarity of NCTN protocols

CIRO’s main function is to support the development of clinical trials exploring new and novel RT techniques that include, for example, proton therapy, stereotactic body RT (SBRT), image-guided RT (IGRT), and the use of imaging to assess response and adapt treatment accordingly. “I also see us continuing to push the envelope on the shorter courses of RT that are achievable using new technology. Our job is to not only make sure it’s done well, but to be able to stand by our results and confirm confidently that this is how patients should be treated,” says Michalski.

The close collaboration between CIRO and the Imaging and Radiation Oncology Core (IROC), a program established to carry out quality assurance (QA) services for the NCTN, plays an integral role in the diffusion of information throughout the NCTN about the use of new RT techniques and technologies. Michalski explains that a significant achievement of CIRO’s first grant year has been working with the leadership of IROC’s six QA centers to gain insight about QA processes and needs across the NCTN and, given associated costs and resources, to determine what can and cannot be accomplished reasonably. This work has led to the establishment of a tiered RT QA approach (see related box). “We don’t have the resources to provide Cadillac QA services for each and every one of our trials,” says Michalski, who explains that an increased focus on site credentialing, as opposed to a review of RT treatment plans for each trial case, ensures that sites are capable of performing the RT per protocol specifications. A key role of the Radiation Oncology Committee’s liaisons to the NRG Oncology disease site committees has been to work with investigators to determine what level of QA is required for any given trial being developed.

Another important member of the CIRO team is the chair of the Medical Physics Subcommittee, Ying Xiao, PhD, FAAPM, professor of radiation oncology at Thomas Jefferson University in Philadelphia. Xiao also emphasizes the close cooperation between CIRO and IROC as being critical for accomplishing the subcommittee’s work.

For example, Ken Ulin, PhD, a physicist with the IROC Rhode Island QA Center, has joined the Medical Physics Subcommittee as a liaison to the NCTN’s Children’s Oncology Group. Ulin is updating the credentialing requirements for total body irradiation in response to new evidence about how the procedure should be conducted. Also, Medical Physics Subcommittee member Fang-Fang Yin, PhD, a professor of radiation oncology at Duke University in Durham, North Carolina, is working closely with the IROC Houston QA Center to develop a simplified, accurate, and uniform QA process for IGRT to be implemented across the NCTN.

Another example of medical physics work underway is the development of SBRT specifications to be used as a template for NRG Oncology protocols involving lung SBRT. Subcommittee members Martha M. Matuszak, PhD, a clinical instructor in the Department of Radiation Oncology at the University of Michigan in Ann Arbor, and Indrin J. Chetty, PhD, director of medical physics at Henry Ford Health System in Detroit, Michigan, are leading this project and soliciting broad input, including from NRG Oncology’s Lung Cancer Committee.

“It has been very exciting to see the investigators champion these and other important projects. One of the ways we hope to make the results of this work available broadly is through publications,” says Xiao. “The contributions from the medical physics community in promoting quality RT in NCTN clinical trials also benefit the cancer treatment community in general—and that’s very rewarding!”

Three-Tiered Quality Assurance Review

1. Pretreatment QA Review: This is required for protocols using new technology or treating a new body site. Treatment plans are reviewed before a patient’s treatment begins. This level of review requires significant commitment on the part of the study physicians and physicists.
2. Retrospective QA Review: Treatment plans are collected and reviewed either after or before a patient’s treatment to provide a performance score or feedback to the site research team.
3. Site Credentialing: This demonstrates that the site research personnel are capable of performing the RT according to the protocol prior to enrolling patients.