Spotlight: NRG Oncology Gastrointestinal Cancer Committee

NRG Oncology’s Gastrointestinal (GI) Cancer Committee is a robust, diverse, and active group with an equally diverse portfolio of research interests and active investigations. Given the variety of disease types and expertise represented, the group’s efforts are divided between the Colorectal and Non-Colorectal Committees. The Colorectal Cancer Committee efforts are orchestrated by Thomas George, MD, FACP (Chair, University of Florida) and Scott Kopetz, MD, PhD, FACP (Vice-Chair, MD Anderson Cancer Center). The Non-Colorectal Cancer Committee efforts are organized by Christopher Crane, MD (Chair, Memorial Sloan Kettering Cancer Center) and Howard Safran, MD (Vice-Chair, Brown University).

Having served on the NSABP’s legacy Colorectal Cancer Committee since 2007, Dr. George was just recently appointed Chair of the NRG Oncology Colorectal Cancer Committee in 2016. “It is an honor and a privilege to serve in this capacity with a clear goal to make meaningful and positive differences for our patients,” says George. With an inherent desire to improve patient outcomes, Dr. George notes that the Colorectal Cancer Committee’s efforts are focused on answering clinically relevant questions through scientifically rigorous and patient-focused clinical trials. Because of the required multidisciplinary cancer care and relative unmet need, rectal cancer trials represent a priority of the...
New Clinical Trials

NRG-GY007: A Phase I/II Study of Ruxolitinib with Front-line Neoadjuvant and Post-Surgical Therapy in Patients with Advanced Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Background
The constellation of diseases commonly referred to as “ovarian cancer,” includes epithelial ovarian, primary peritoneal and fallopian tube carcinomas, and is diagnosed in approximately 22,000 women in the United States annually.1 More sobering is the projection that approximately 14,000 will die of this disease annually.2 Based on this high relative mortality to incidence rate, ovarian cancer ranks as the third most lethal malignancy affecting women.1 Its lethality has been attributed largely to advanced stage at diagnosis and absence of effective screening for potentially early stage disease.1 In addition, acquired drug resistance and the lack of specificity for mechanisms of disease progression.1

The NRG-GY007 trial was developed to address the need for new agents with activity against ovarian cancer, primarily those targeting the mechanisms of disease progression. The phase I/II study will assess the safety and efficacy of ruxolitinib in combination with conventional neoadjuvant and post-surgical chemotherapy and as maintenance for patients with high grade epithelial ovarian, primary peritoneal, or fallopian tube cancer.

According to Robert A. Burger, MD, the Study Chair for the trial, “NRG-GY007 is the first of a series of trials utilizing a novel trial design that will allow more efficient and hypothesis driven evaluation of new agents for ovarian cancer. This design capitalizes on the ability to evaluate specific, early pharmaco-dynamic changes in tumors to identify populations of women likely to benefit in higher order trials and clinical practice and is aligned with the 2015 NCI Gynecologic Cancer Steering Committee Strategic Priorities.”

Although ruxolitinib has yet to be evaluated in patients with epithelial ovarian cancer, the combination of ruxolitinib with a variety of cytotoxic chemotherapy regimens has been under investigation in a number of ongoing clinical trials for solid tumors in other disease sites.

Primary Objective
Phase One: To determine whether treatment with ruxolitinib in combination with conventional neoadjuvant and post-surgical chemotherapy is safe and tolerable in the primary therapy for epithelial ovarian, fallopian tube, or primary peritoneal carcinoma.

Phase Two: To demonstrate whether treatment with ruxolitinib in combination with conventional neoadjuvant and post-surgical chemotherapy results in a prolonged progression-free survival when compared to chemotherapy alone, in primary therapy for epithelial ovarian, fallopian tube, or primary peritoneal carcinoma.

Secondary Objectives (Summary)
Phase One: To determine whether treatment with ruxolitinib in combination with conventional neoadjuvant and post-surgical chemotherapy is safe and tolerable in the primary therapy for epithelial ovarian, fallopian tube, or primary peritoneal carcinoma.

Phase Two:
• Samples will be collected for subsequent translational endpoints to determine the impact of ruxolitinib in combination with chemotherapy on progression-free survival.
• To determine whether treatment with ruxolitinib in combination with conventional chemotherapy is associated with total gross resection rate at time of interval cytoreductive surgery.
• To determine whether treatment with ruxolitinib in combination with conventional chemotherapy is associated with complete pathologic response defined at interval cytoreductive surgery.
• To demonstrate whether treatment with ruxolitinib in combination with conventional chemotherapy results in an improvement in overall survival in primary management of epithelial ovarian, fallopian tube, or primary peritoneal carcinoma.

Target Accrual
Phase One: 28 patients
Phase Two: 130 patients

Patient Population
Patients with clinically and radiographically suspected FIGO stage III or IV epithelial ovarian, primary peritoneal, or fallopian tube cancer, high grade, for whom the plan of management will include neoadjuvant chemotherapy (NACT) with interval tumor reductive surgery (TRS) who

1 “Epithelial Ovarian Cancer,” in Principles and Practice of Gynecologic Oncology, Sixth Edition, edited by Barakat RR; Berchuck A; Markman M; Randall ME. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia, 2013
New Clinical Trials (continued)

have undergone biopsies for histologic confirmation.

**Schema**

**Phase One:**

- Candidate for Neoadjuvant Chemotherapy (NACT)
  Receives Histologic Diagnosis and Imaging Guided Core or Laparoscopic Biopsies
- Pathology consistent with epithelial OV/FT/PP Cancer

<table>
<thead>
<tr>
<th>3 Cycles of Experimental Regimen</th>
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<tbody>
<tr>
<td>Paclitaxel 80 mg/m² IV D1, 8, 15 (P)</td>
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<tr>
<td>Carboplatin AUC 5 or 6 IV D1 (C)</td>
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<tr>
<td>Ruxolitinib (RUX) at 10 or 15 mg</td>
</tr>
<tr>
<td>PO BID 12 hours apart Days 1-21</td>
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The first dose must be at least 1 hour prior to the Paclitaxel.

- Tumor Reductive Surgery (TRS)

<table>
<thead>
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<tbody>
<tr>
<td>P + C + RUX</td>
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</table>

**Maintenace Ruxolitinib**

Will be evaluated only in participants who complete all 6 cycles of chemotherapy with RUX, until disease progression, unacceptable toxicity, or voluntary withdrawal.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Paclitaxel 80 mg/m² IV D1, 8, 15 (P)</td>
</tr>
<tr>
<td>Carboplatin AUC 6 IV D1 (C)</td>
</tr>
</tbody>
</table>

**Phase Two:**

- Candidate for Neoadjuvant Chemotherapy (NACT)
  Receives Histologic Diagnosis and Imaging Guided Core or Laparoscopic Biopsies
- Pathology consistent with epithelial OV/FT/PP Cancer

<table>
<thead>
<tr>
<th>3 Cycles of Reference Regimen</th>
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<tbody>
<tr>
<td>Paclitaxel 80 mg/m² IV D1, 8, 15 (P)</td>
</tr>
<tr>
<td>Carboplatin at phase II dose IV D1 (C)</td>
</tr>
<tr>
<td>Ruxolitinib (RUX) at determined phase II dose</td>
</tr>
<tr>
<td>PO BID 12 hours apart Days 1-21</td>
</tr>
</tbody>
</table>

The first dose must be at least 1 hour prior to the Paclitaxel.

- Tumor Reductive Surgery (TRS)

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<tr>
<td>P + C + RUX</td>
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NRG-CC003: A Randomized Phase II/III Trial of Prophylactic Cranial Irradiation with or without Hippocampal Avoidance for Small Cell Lung Cancer

**Background**

Intracranial failure is a frequent problem in patients with small cell lung cancer (SCLC). The burden of brain metastases impacts on quality and length of survival. Multiple clinical trials of prophylactic cranial irradiation (PCI) in patients with limited-stage SCLC (LS-SCLC) and extensive stage SCLC (ES-SCLC) have consistently shown a reduction in the incidence of brain metastases and prolongation in survival with the use of PCI. These data provide compelling evidence for the use of PCI in SCLC.

In spite of clinical evidence demonstrating an overall survival benefit from PCI, a recent study from Memorial Sloan-Kettering Cancer Center demonstrated that 40 percent of eligible LS-SCLC patients do not receive PCI. Concerns about cognitive toxicity from PCI—on the part of both patient and physician—were found to be the primary reasons for not receiving PCI, underscoring the importance of studying novel approaches to mitigating PCI-associated cognitive toxicity. Building upon extensive preclinical and clinical data supporting the memory-specificity and radiosensitivity of the hippocampal neural stem cell compartment, RTOG 0933 demonstrated highly promising memory-preservation results with the application of IMRT techniques to conformally avoiding the hippocampus during cranial irradiation. NRG-CC003 was proposed as a placebo-controlled, randomized study of SCLC patients receiving PCI that addresses the hypothesis that hippocampal avoidance may prevent radiotherapy-induced memory toxicity.

**Primary Objective**

**Randomized Phase II Component (Non-Inferiority):** To determine whether the 12-month intracranial relapse rate following HA-PCI is non-inferior to the rate following PCI for patients with SCLC.

“Despite the evidence for an overall survival benefit from PCI, 40% of eligible patients do not receive it due to concerns of cognitive toxicity. NRG-CC003 will address the hypothesis that hippocampal avoidance may prevent radiotherapy-induced memory toxicity.”

VINAI GONDI, MD
NRG-CC003 Principal Investigator

continued
New Clinical Trials (continued)

Phase III Component (Efficacy): To determine whether HA-PCI reduces the likelihood of 6-month deterioration from baseline in HVLT-R delayed recall compared to PCI for patients with SCLC.

Secondary Objectives (Phase III)
• To compare time to cognitive failure, as measured by a battery of tests (HVLT-R, COWA test, and TMT Parts A and B), after PCI versus HA-PCI in SCLC.
• To compare time to cognitive failure as separately measured by each test (HVLT-R for Total Recall and Delayed Recognition, COWA test, and TMT Parts A and B), after PCI versus HA-PCI for SCLC.
• To compare patient-reported cognitive functioning and other quality of life domains (assessed by the EORTC QLQ-C30 and BN20) between PCI versus HA-PCI for patients with SCLC.
• To compare overall survival after PCI versus HA-PCI for patients with SCLC.
• To compare 12-month intracranial relapse rate (at completion of phase III) and time to intracranial relapse after PCI vs. HA-PCI for patients with SCLC.
• To evaluate adverse events according to CTCAE criteria.
• To correlate changes in HRQoL domains with changes in cognitive testing outcomes following PCI versus HA-PCI.
• To assess cost-effectiveness of HA-PCI (MRT) and PCI (3DCRT) using the EQ-5D-5L.

Exploratory Objectives
• To collect serum and whole blood for future translational research analysis.
• To evaluate baseline MR imaging biomarkers of white matter injury and hippocampal volumetry as potential predictors of cognitive decline and differential benefit from HA-PCI as compared to PCI.
• To compare levels of hopefulness between PCI versus HA-PCI for patients with SCLC.

Target Accrual
Phase Two: 164 patients
Phase Three: 302 patients

Patient Population
Patients with histologic proof or unequivocal cytologic proof (fine needle aspiration, biopsy or two positive sputa) of SCLC within 250 days prior to Step 1 registration; Zubrod performance status 0-2; Patients who are primary English or French speakers are eligible.

Schema

Histologic or unequivocal cytologic proof of SCLC

STEP 1 REGISTRATION

STEP 2 REGISTRATION/RANDOMIZATION
Baseline neurocognitive assessment: HVLT-R, TMT, COWA (required)
Note: Neurocognitive assessments can be uploaded at the time of Step 1 Registration

STRATIFICATION
Stage: Limited vs. Extensive
Age <60 years old vs. ≥60 years old
Planned Concurrent Memantine Use: Yes vs. No

Arm 1
PCI Alone (25 Gy in 10 Fractions)

Arm 2
PCI with Hippocampal Avoidance using IMRT (25 Gy in 10 Fractions)

NRG-HN003: A Phase I and Expansion Cohort Study of Adjuvant Cisplatin, Intensity-Modulated Radiotherapy, and MK-3475 (Pembrolizumab) in High-Risk Head and Neck Squamous Cell Carcinoma (HNSCC)

Background
Head and neck squamous cell carcinoma (HNSCC) is the 6th leading cancer worldwide. Despite advances in cancer detection and multimodality treatments including surgery, radiation therapy (RT), and chemotherapy, the 5-year overall survival (OS) is only 40-60 percent. Modest improvements in OS have been largely attributable to the emergence of human papillomavirus (HPV)-related HNSCC, which involves younger and lower-risk populations. Nevertheless, 80 percent of HNSCC diagnoses worldwide remain secondary to the environmental carcinogens, tobacco and alcohol. The current standards of care for the adjuvant management of locally advanced, HPV-negative HNSCC are determined by pathologic risk. Specifically, the adjuvant standard for patients who demonstrate 1 or more high-risk pathologic features, including a positive surgical margin or extracapsular nodal extension, is concurrent cisplatin-radiotherapy, which improved disease-free survival (DFS), and locoregional control (LRC) compared with RT alone in the landmark EORTC 22931 and RTOG 9501 trials. Despite this advance, patients with high-risk HPV-negative disease have a 3-year DFS of only 30-50 percent. Poor outcomes persist despite intensification with altered fractionation, multi-drug induction, or EGFR-targeted monoclonal antibodies (mAb). For HPV-negative patients, new intensification approaches are a major unmet need. Due to their distinct biology, favorable prognosis, and low event rate, patients with HPV-positive HNSCC are excluded from clinical trials evaluating adjuvant intensification approaches in the high risk HPV-negative population.

continued
New Clinical Trials (continued)

NRG-HN003 is an open-label, dose-finding phase I trial with a planned expansion cohort, evaluating the safety and feasibility of the addition of the PD-1 mAb MK-3475 (pembrolizumab) to standard adjuvant therapy with conventionally fractionated IMRT and concurrent weekly cisplatin in patients with high-risk, HPV-negative HNSCC. The trial will proceed in two stages: Phase I (dose-finding), which will enroll patients to descending dose levels and determine the recommended phase II dose (RP2D) for the combination based upon DLT; and an expansion cohort, which will improve estimates of the safety and feasibility of the RP2D within the NCTN protocol organization setting.

Primary Objective
To determine the RP2D for the combination of MK-3475 (pembrolizumab) and standard, adjuvant cisplatin-radiotherapy in patients with high-risk, HPV-negative HNSCC, based upon dose-limiting toxicity (DLT).

Secondary Objectives
- To describe 1-year DFS, OS, locoregional failure (LRF), and rate of distant metastases following treatment with adjuvant cisplatin-radiotherapy and MK-3475 (pembrolizumab).
- To describe the toxicity of the combination of cisplatin-radiotherapy and MK-3475 (pembrolizumab) according to CTCAE v. 4, including immune-related adverse events (AEs).
- To describe the relationship between baseline PD-L1 expression and 1-year DFS.
- To describe baseline immune-inflammatory biomarkers in both tumor and tumor-infiltrating lymphocytes (TILs), and correlate them with 1-year DFS.
- To describe baseline and change in expression of peripheral immune-inflammatory biomarkers, including a panel of candidate tumor antigen (TA)-specific memory T cells, and correlate with 1-year DFS.

Target Accrual
32 minimum to 56 maximum patients

Patient Population
Patients with stage III-IVb, high-risk squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx; patients with oropharyngeal cancer must be p16-negative.

Schema

**Step 1 Registration**: For oropharynx cancer patients, the institution will do p16 testing and analysis of patient pathology material and must submit H&E and p16 stained slides to the Biospecimen Bank at UCSF for central review prior to Step 2 Registration. Oral cavity, larynx and hypopharynx cancer patients proceed to Step 2 Registration.

**Note**: A paraffin block or punch is required for all patients for retrospective testing of PD-L1.

<table>
<thead>
<tr>
<th>PHASE 1 DOSE FINDING #</th>
<th>EXPANSION COHORT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose Level 3</strong>, n=12 (Starting Dose)</td>
<td><strong>Expansion Cohort</strong>, n=20</td>
</tr>
<tr>
<td>MK-3475 (pembrolizumab):</td>
<td>At a to-be-specified dose and schedule for the combination of MK-3475 (pembrolizumab), cisplatin and IMRT.</td>
</tr>
<tr>
<td>- Loading Dose: 200mg IV, Week -1</td>
<td></td>
</tr>
<tr>
<td>- Concurrent: 200mg IV, Weeks 3 and 6 of CRT</td>
<td></td>
</tr>
<tr>
<td>- Maintenance: 200mg IV q3 Weeks for 6 doses (Week 9, 12, 15,18,21,24)</td>
<td></td>
</tr>
<tr>
<td>Cisplatin, 40mg/m²/week for 6 doses, starting week 1 of IMRT (Weeks 1-6)</td>
<td></td>
</tr>
<tr>
<td>IMRT, 60 Gy over 30 fractions, 5 fractions per week (Weeks 1-6)</td>
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</tbody>
</table>
New Amendment

NRG-GU001: A Randomized Phase II Trial Of Postoperative Adjuvant IMRT Following Cystectomy For pT3/pT4 Urothelial Bladder Cancer

Update on NRG-GU001: Amendment 2 Forthcoming
Forthcoming in the next month, Amendment 2 of NRG-GU001 will widen eligibility and increase accrual. Four valuable changes have been made and are highlighted here. First, tight enrollment times currently in place will be expanded, allowing for the inclusion of as many patients as is practical. Second, the amendment addresses an ineligibility factor. Patients with remote, unrelated malignancies and those with prior chemotherapy for other malignancies will no longer be deemed ineligible. Third, imaging assessments in follow up have been revised such that no follow-up imaging that exceeds current standards of care will be required.
Finally, and most importantly, the amendment will include patients with neobladders. Subsequent to the activation of NRG-GU001, there were two important developments to warrant including this patient population. First, an international contouring consensus has been developed for radiotherapy target delineation post cystectomy. This guideline emphasizes that the cystectomy bed requires irradiation only if margins are positive. Thus, in the vast majority of patients (ie, margin negative), the target consists of the pelvic node sidewall volumes alone, greatly limiting the radiation dose exposure to a neobladder. Second, there are a French and an American (USC) clinical experience with post cystectomy radiotherapy given to patients with a neobladders that demonstrates the safety of this irradiation. The fact that an increasing number of patients are getting a neobladder, coupled with target delineation and neobladder irradiation safety data, makes the addition of this patient population appropriate.

Background
Pelvic tumor recurrence following contemporary cystectomy has traditionally been considered a relatively infrequent event. Cagiannos and Morash (2009) compiled 8 institutional series between 1977 and 2006 reporting local recurrence rates ranging from 3.9 to 29%. These series have underestimated the true risk of pelvic relapse for a variety of reasons including: exclusion of patients who have also developed distant metastases, using simple numerator/denominator crude risk calculation rather than cumulative incidence rates, not calculating risk according to T stage and excluding pelvic relapses if they have not been biopsied. Herr (2004), reporting the surgical parameters in the neoadjuvant chemotherapy SWOG 8710 trial, demonstrated that despite requiring biopsy confirmation the crude risk of developing local recurrence following cystectomy in pT3/4 disease was 32%. Given that patients with locally advanced cancer have a high rate of systemic metastases, it is important to determine the impact of pelvic radiotherapy not only on pelvic relapse, but also on overall disease-free survival (DFS). NRG-GU001 will look for a 10% increase in DFS, the signal that will warrant proceeding to a confirmatory phase III trial, only if the primary pelvic failure and secondary DFS endpoints are met with acceptable toxicity.

Primary Objective
To evaluate the ability of post-cystectomy adjuvant radiotherapy to safely reduce pelvic tumor recurrence

Secondary Objectives
• To increase in disease-free survival
• To evaluate toxicity of adjuvant pelvic radiotherapy

Target Accrual
185 Patients

Patient Population
Patients with pT3/pT4 pN0-2 urothelial (either pure urothelial or primary urothelial mixed with other subtypes) bladder cancer following radical cystectomy with ileal conduit.

Updated Schema for Amendment 2

PATIENT POPULATION
Patients with pT3/pT4 pN0-2 urothelial (either pure urothelial or primary urothelial mixed with other subtypes) bladder cancer following radical cystectomy

STRATIFICATION
Neoadjuvant preoperative or postoperative adjuvant chemotherapy vs. No chemotherapy
Pelvic relapse risk category: Intermediate vs. High

REGISTRATION
Within 105 days of radical cystectomy

TIMING OF RANDOMIZATION
Patients who will not receive postoperative adjuvant chemotherapy:
Within 14 days of registration
Patients who will receive postoperative adjuvant chemotherapy:
Within 14 days of completion of the chemotherapy

Arm 1: Standard Arm
No radiotherapy

Arm 2: Experimental Arm
Postoperative adjuvant IMRT radiotherapy
50.4 Gy/28
Semiannual Meeting Highlights

The NRG Oncology Semiannual Meeting will take place July 14 – 16 in Dallas, Texas. This meeting 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. The following are a few of the highlights:

Cultural Competency Workshop
Friday, July 15, 2016; 11:00AM-1:00PM

Dr. Marvella Ford, Associate Director of Cancer Disparities, Hollings Cancer Center, Medical University of South Carolina and Professor, Department of Public Health Sciences will speak July 15, 11:00 AM -1:00 PM on Cultural Competency in Clinical Trials during the NRG Oncology Semiannual Meeting in Dallas, Texas.

Dr. Ford is the PI on a NIH funded center grant titled “South Carolina Disparities Research Center (SC CaDRe)”. The goal of the SC CaDRe is to expand cancer disparities research in South Carolina while cultivating a diverse network of cancer researchers. The grant provides funding to train underrepresented students and junior faculty in cancer research methods. She is also a PI on a NIH-funding grant to increase the participation of diverse participants in cancer research and leads a DOD and NIH-funded summer undergraduate cancer research training program in collaboration with three historically black colleges/universities (HBCUs) in South Carolina. She is the author of more than 75 published scientific articles.

Dr. Ford will address how culture influences health problems, how symptoms are expressed and discussed and how health care information is received. Health care decision-making can also be influenced by demographic factors. In order to provide culturally competent cancer care, healthcare providers must value diversity, recognize the dynamics of cultural interactions, and consider solutions that take those diverse interactions into consideration. As less than 1% of underrepresented minority groups are currently enrolled in clinical trials, improving communication between patients and their treatment team would be of benefit. This could be accomplished by gaining a better understanding of how patients perceive illness and treatment, educating patients and family members about symptom management and how to better communicate with their treatment team.

Immunotherapy and Immune Modulation Workshop
Friday, July 15, 2016; 11:00AM-12:30PM

Patrick Soon-Shiong, Chairman of the Chan Soon-Shiong Family Foundation, Chairman and CEO of the Chan Soon-Shiong Institute of Molecular Medicine and Chairman and CEO of NantKwest along with Shahrooz Rabizadeh, PhD, Chief Scientific Officer at NantOmnics, LLC and NantBioScience, Inc. will be presenting during the Immunotherapy and Immune Modulation at the NRG Oncology Semiannual Meeting. Soon-Shiong and Rabizadeh will be focusing on clarifying the Cancer Moonshot 2020 Initiative.

NRG Scientific Session
Friday, July 15, 2016; 8:00AM-10:00AM

Do not miss out on the opportunity to learn more about the NCI’s National Clinical Trial Network (NCTN) Study Champion Program and its implementation during the NRG Scientific Session at the NRG Oncology Semiannual Meeting. Presenters will explore the interim analysis results of the NCI’s Molecular Analysis for Therapy Choice (NCI-MATCH) Trial, the interim joint analysis of the ABC phase III trials comparing docetaxel + cyclophosphamide vs anthracycline/taxane-based chemotherapy regimens in women with high-risk, HER-2-negative breast cancer, the NRG-RTOG 9601 phase III trial in prostate cancer patients, mutations in homologous recombination genes and response to treatment in NRG-GOG 218, and the correlation between the severity of cetuximab-induced skin rash and clinical outcome for head and neck cancer patients.

NRG Oncology General Session
Friday, July 15, 2016; 1:00PM-2:00PM

The NRG Oncology General Session will occur at the Lone Star B Conference Center on the second floor Friday, July 15, 2016 from 1-2PM. Attendees can participate in a question and answer session for the NCTN grant recOMPETITION and a presentation on the NCI NCTN Core Correlative Sciences Committee (CCSC). Also, the Joan K. Mauer Memorial Quality Assurance Award and the 2016 Top Accruing Institutions will be presented along with a membership update from NRG Oncology.

Join the conversation on Twitter!

Are you attending the NRG Oncology Semiannual Meeting in Dallas July 14-16? Use the hashtag – #NRGMtg16 to stay up-to-date on trending topics regarding the meeting and engage with other attendees on the events taking place.
NRG Oncology Featured Publications

This 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.

From the Gastrointestinal Cancer Committee
Clinical Outcome From Oxaliplatin Treatment in Stage II/III Colon Cancer According to Intrinsic Subtypes

Oxaliplatin added to fluorouracil plus leucovorin therapy for patients with colon cancer has been shown to provide significant benefit for disease-free survival. However, due to the fact that oxaliplatin is associated with acute and chronic neurotoxic effects, there is a need for identifying patients that would actually benefit from oxaliplatin. A secondary analysis of the NRG Oncology randomized clinical trial NSABP C-07, led by Kay Pogue-Geile, PhD, Associate Director of Molecular Profiling, Department of Pathology, NSABP, and published in the Journal of the American Medical Association (JAMA Oncology) on June 6th, tested the hypothesis that molecular subtypes of colon cancer would be associated with differential prognosis and benefit from the oxaliplatin regimen.

The NSABP C-07 trial accrued 1,729 participants from February 2000 through November 2002. Participants were divided into discovery (n = 848) and validation (n = 881) cohorts based on the order of tissue block submission. A reestimated centroid using 72 genes was used to determine Colorectal Cancer Assigner subtypes and their association with oxaliplatin benefit in the discovery cohort. The validation cohort was examined with a locked-down algorithm for subtype classification and statistical analysis plan. Post hoc analysis included examination of the entire cohort with Colorectal Cancer Assigner, Colorectal Cancer Subtype (CCS), and Consensus Molecular Subtype (CMS) methods.

Of the 1,729 patients included in the trial, participants with stage III disease with an enterocyte subtype showed a statistically significant benefit from oxaliplatin in the discovery cohort (hazard ratio, 0.22 [95% CI, 0.09-0.56]; P = .001 [N = 65]), however no statistically significant benefit was observed in the validation cohort (hazard ratio, 0.53 [95% CI, 0.22-1.24]; P = .14 [N = 70]). The stemlike subtype was associated with poor prognosis and lack of benefit from oxaliplatin treatment (HR, 0.99 [95% CI, 0.73-1.34]; P = .96 [N = 367]). Examination of the different subtyping methods shows that all three methods robustly identified patients with poor prognosis (stemlike, CCS-3, and CMS-4) in both stage II and III.

“These results indicate that patients with stemlike tumors are appropriate for future clinical trials testing experimental therapies because stemlike tumors were robustly identified and associated with a poor prognosis regardless of stage or chemotherapy regimen,” says Dr. Pogue-Geile.

This study also offers evidence that subtypes differ with degree of benefit from oxaliplatin, although this finding must be validated in an independent cohort before it can be implemented clinically.

From the Breast Cancer Committee
Prognostic Impact of the Combination of Recurrence Score and Quantitative Estrogen Receptor Expression (ESR1) on Predicting Late Distant Recurrence Risk in Estrogen Receptor-Positive Breast Cancer After 5 Years of Tamoxifen

Results of the clinical trials NSABP B-28 and B-14, published in the Journal of Clinical Oncology on May 23rd, determined that utilizing the 21-Gene Recurrence Score (RS) assists in the predicting late (>5 years) distant recurrence (LDR) in patients with stage I and II breast cancer within high and low quantitative estrogen receptor (ESR1) expressing groups.

“Trial NSABP B-28 and B-14 are providing great insight into the value of extended tamoxifen therapy merits evaluation in patients with intermediate and high RS with higher ESR1 expression at initial diagnosis,” says lead author Norman Wolmark, MD, NRG Oncology Group Chair and Chairman and Principal Investigator of the NSABP.

During the trials, RS was assessed in chemotherapy/tamoxifen-treated, strong receptor (ER)-positive, node-positive National Surgical Adjuvant Breast and Bowel Project (NSABP) B-28 patients and tamoxifen-treated, ER-positive, node-negative B-14 patients. The association of the RS with the risk of distant recurrence (DR) 0 to 5 years and those at risk over 5 years was evaluated. An ESR1 expression cut point for patients was optimized in B-28 and tested in B-14.

The median follow-up for NSABP B-28 was 11.2 years, whereas the follow-up for NSABP B-14 was 13.9 years. B-28 included 1,065 patients and, of those patients, 36 percent had low (<18), 34 percent had intermediate (18 to 30), and 30 percent had high (≥31) RS. B-14 included 668 patients and, of those patients, 51 percent had low, 22 percent had intermediate, and 27 percent had high RS. The median ESR1 expression by reverse transcriptase polymerase chain reaction (RT-PCR), used to detect RNA expression, for B-28 was 9.7 normalized expression cycle threshold units (CT), and for B-14 10.7

continued
Followed by 6 cycles of PCV. Before treatment initiation, images, patients were randomized to RT alone or RT presence or absence of contrast-enhanced preoperative histology, Karnofsky Performance Status, and the biopsy to be eligible. Following stratification by age, 18 to 39 years must have had a subtotal resection or oligodendroglioma, or oligoastrocytoma. Patients aged 2002, had histologically confirmed grade 2 astrocytoma, the study's 251 eligible patients, enrolled from 1998 to 2002, had histologically confirmed grade 2 astrocytoma, oligodendroglioma, or oligoastrocytoma. Patients aged 18 to 39 years must have had a subtotal resection or biopsy to be eligible. Following stratification by age, histology, Karnofsky Performance Status, and the presence or absence of contrast-enhanced preoperative images, patients were randomized to RT alone or RT followed by 6 cycles of PCV. Before treatment initiation, tumor samples underwent central pathology review and were prepared for correlative laboratory studies. Tumor IDH1-mutational status was assessed through immunohistochemistry with the mutation-specific monoclonal antibody IDH1 R132H. The PFS and OS distributions were compared using the log rank test, and Cox proportional hazard models were used to identify prognostic variables.

At a median follow-up time of 11.9 years, 67 percent of enrolled patients were identified as having tumor progression, and 55 percent of patients had died. Patients in the RT plus PCV arm had longer median survival times compared with those in the RT alone arm (13.3 vs. 7.8 years, respectively; p=0.003). Median PFS time for patients receiving RT plus PCV versus RT alone was 10.4 years and 4.0 years, respectively. Ten-year PFS and OS rates for patients in the RT plus PCV arm versus those in the RT alone arm were 51 percent versus 21 percent and 60 percent versus 40 percent, respectively. For both PFS and OS distributions, a difference between treatment arms became apparent only after 2 to 4 years following randomization. The favorable prognostic variables identified included the RT plus PCV arm, oligodendroglioma histology, IDH1 R132H mutation, and younger age.

Toxicity was greater in the PCV arm, as expected and consistent with those of any patients receiving multiagent chemotherapy regimens. The most common toxicities were fatigue, anorexia, nausea, and vomiting, which were mostly grade 1−2 in severity with the exception of grade 3−4 neutropenia.

“Our results indicate that initial therapy of RT followed by PCV is necessary to achieve longer survival in patients with grade 2 glioma and that salvage therapy at relapse after RT alone is less effective,” says Buckner. “It has also been hypothesized that other genetic alterations may be responsible for a small subset of patients whose glial brain tumors are chemotherapy-resistant. However, radiation therapy plus PCV appears to represent the most effective treatment identified to date for the majority of patients with grade 2 glioma,” concludes Buckner.

“These results provide further clarification about how the histopathologic differences among low-grade gliomas correlate with their biologic behavior and progression. They also shed light on the most effective role and timing of radiation therapy and chemotherapy in prolonging progression-free and overall survival and minimizing morbidity in the younger age group of patients diagnosed with these brain tumors,” says Walter J. Curran, Jr, MD, the report’s senior author, NRG Oncology Group Chairman, and Executive Director of the Winship Cancer Institute.

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continued on page 11
NRG-NSABP B-49 Abstract Named “Best of ASCO”
Dr. Joanne Blum presented the interim joint analysis of the ABC phase III trials at the 2016 ASCO meeting on June 4 in Chicago. The abstract, "Interim joint analysis of the ABC (anthracyclines in early breast cancer) phase III trials (USOR 06-090, NSABP B-46-I/USOR 07132, NSABP B-49 [NRG Oncology]) comparing docetaxel + cyclophosphamide (TC) v anthracycline/taxane-based chemotherapy regimens (TaxAC) in women with high-risk, HER2-negative breast cancer," has been named a "Best of ASCO" abstract and will be featured at Best of ASCO meetings in Chicago, Washington, DC and San Diego this summer.

NRG-NSABP C-07 Results Presented at 2016 ASCO Meeting
Kay Pogue-Geile, PhD, Associate Director of Molecular Profiling, Department of Pathology, NSABP, presented results during the 2016 American Society of Clinical Oncology Annual Meeting in Chicago during a gastrointestinal (colorectal) cancer session.

Colon cancer is known to be a heterogeneous disease involving many differences at both the clinical and molecular levels. Previous research has demonstrated that gene expression profiling of colorectal cancer tumors can be used to classify CRC into different subtypes. NSABP investigators have tested the association of these tumor subtypes with prognosis and treatment benefit in patients enrolled in NSABP C-07, a clinical trial that demonstrated the benefit of adding oxaliplatin to 5-fluorouridine plus leucovorin. The importance of identifying patients who actually benefit from oxaliplatin is important because oxaliplatin is associated with acute and chronic neurotoxicity. At the ASCO meeting, Kay Pogue-Geile, PhD, presented evidence showing that colon cancer subtypes differ not only with respect to their prognosis but also with respect to their response to chemotherapy. This study validates the observation that patients with stem-like tumors were robustly identified and that such tumors are associated with a very poor prognosis, regardless of stage or chemotherapy regimen, indicating that patients with stem-like tumors are appropriate for future clinical trials using new therapeutic approaches.

NRG Oncology Presents Results of the RTOG 0825 Study on Germline Polymorphisms in Relation to Glioblastoma at ASCO 2016
Glioblastoma (GBM) is the most common primary brain tumor among adults with a median survival of 12-14 months for patients diagnosed with this type of cancer. Presented at the 2016 American Society for Clinical Oncology (ASCO) Annual Meeting, NRG Oncology conducted the trial RTOG 0825 to evaluate the use of bevacizumab in patients with newly diagnosed GBM. Since bevacizumab is commonly associated with hypertension and vascular thrombotic events, this study assessed the risk and validated prediction models for vascular toxicity. The final clinical model shows that hypertension was highly associated with bevacizumab and the accuracy of risk assessment was enhanced after including polymorphisms in the model, whereas thrombosis was not related to bevacizumab treatment. The results provide the potential to screen patients and determine those at greater risk as treatment moves towards both tumor and patient precision medicine.

NRG-RTOG 0525 and 0825 Establishes Nomogram to Estimate Individualized Survival Probabilities for Patients with Newly Diagnosed Glioblastoma
The study NRG Oncology/RTOG 0525 and 0825 built and independently validated a nomogram to estimate individualized survival probabilities for patients with newly diagnosed glioblastoma (GBM) by using data from two independent NRG Oncology/Radiation Therapy Oncology Group (RTOG) trials. Nomograms are frequently used for individualized estimation of prognosis; however, this approach has only been applied to GBM once before (eORTC 26981/22981-NCIC) and this was exclusively internally validated. These trials, which were presented at the 2016 American Society for Clinical Oncology (ASCO) Annual Meeting, concluded that a nomogram for patients with newly diagnosed GBM could be useful in counseling patients regarding their treatment decisions and optimizing therapeutic approaches.

New Developments in Brain Tumor Research Presented at the 2016 American Society for Clinical Oncology Annual Meeting
NRG-RTOG 9402, 9802, and 9813 were recently highlighted for their efforts in brain tumor research at the 2016 American Society for Clinical Oncology (ASCO) Annual Meeting. The results of these studies are providing information to the radiation oncology community on the prognostic value and treatment of mutations associated with brain cancer. The randomized, multi-center NRG-RTOG 9402 trial was initiated to determine whether there are specific genetic alterations that can distinguish patients who benefit from the addition of chemotherapy PCV treatment from those who do not. Initially, the study showed a significant survival benefit in patients with 1p/19q co-deleted anaplastic
oligodendrogliomas (AO) who received both radiation therapy (RT) and PCV versus RT alone. The results did not identify a distinct genetic signature that correlates with improved benefit from chemotherapy with PCV in patients with newly diagnosed 1p/19q co-deleted AO; however, differences in alterations of ESX1 warrant further investigation.

NRG-RTOG 9802 examined the prognostic significance of mutations with IDH1/2, ATRX, CIC, FUBP1, and the TERT promoter in a prospective phase III study of high-risk low-grade gliomas (LGGS) using multivariate analyses (MVAs). This is the first study to examine the prognostic effects of these mutations using MVA in a grade II astrocytoma cohort with prospectively-collected, well-annotated clinical data. This study confirms that the prognostic value of the TERT promoter, IDH, and CIC mutations and suggests that TERT and CIC may provide additional information beyond IDH.

The study NRG-RTOG 9813 examined the prognostic value of mutations within IDH1/2, ATRX, CIC, FUBP1, and the TERT promoter in a phase III study of grade III astrocytomas using MVAs. Similar to NRG-RTOG 9802, this is the first study to examine the prognostic effects of these mutations using MVA in a grade III astrocytoma cohort with prospectively-collect, well-annotated clinical data. This study underscores the prognostic significance of IDH and ATRX. Efforts are ongoing to increase the sample size and perform predictive analyses for this study and for NRG Oncology/RTOG 9802.

At ASCO 2016 (continued)

Institute of emory University in Atlanta.

From the Lung Cancer Committee
NRG RTOG 0617 Shows Survival Correlation for Low versus High Enrolling Institutions for Patients with LA-NSCLC
Lung cancer is the leading cause of cancer-related death in the United States and is estimated to have contributed to 221,200 new cases and 158,040 deaths in 2015 alone. A secondary analysis of NRG Oncology’s clinical trial RTOG 0617, published in volume 108, issue 9 of the Journal of the National Cancer Institute, was initiated in an effort to evaluate the effect of institution accrual volume on clinical outcomes among patients receiving chemoradiation for locally advanced non-small cell lung cancer (LA-NSCLC). The study showed that patients treated at institutions with higher trial accrual volume on a phase III trial had statistically significant longer overall survival compared with patients treated at low-volume centers.

“The overall survival difference between patients treated at high-volume centers versus low-volume centers was greater than 10% at two years, which is a substantial finding for LA-NSCLC,” says the study’s lead author, Bree Eaton, MD of the Winship Cancer Institute of Emory University in Atlanta. “It is suspected that the effect on overall survival may be a reflection of both improved disease control and better management or prevention of adverse effects.”

Four hundred and ninety-five eligible patients were randomly assigned and treated at 180 different institutions. The range of accrual for low-volume centers (LVCs) was one to three patients, whereas high-volume centers (HVCs) were four to 18 patients. RT was administered according to protocol specifications for target volume definition and treatment delivery. Kaplan-Meier (KM) estimates of overall survival at two years were 55.5 percent for the HVC cohort compared with 43.9 percent for the LVC cohort. HVC remained significantly associated with a lower risk of death.

“These results provide further clarification on the differences in outcomes between higher and lower accruing sites and it also shapes the way the radiation oncology community approaches the treatment of LA-NSCLC,” says Walter J. Curran, Jr., MD, an NRG Oncology Group Chair and Executive Director of the Winship Cancer Institute of Emory University.

Protocol Support Committee
Mentorship Working Group Update
The NRG Mentorship Working Group has been working diligently to develop a “Welcome To New Members” resource packet. This online packet was designed to make the introduction to NRG Oncology as smooth as possible by providing information regarding specific processes and contacts to be used when conducting NRG Oncology clinical trials. The information is intended to assist new members in understanding how NRG Oncology trials operate and who to contact when there are questions or difficulties. The packet was recently posted on the NRG website.

The PSC Mentorship Working Group has also been working on the development of the Mentor Program. This is an exciting opportunity for members to become involved as we will be looking for Mentors to assist once the program is ready for activation. Stay tuned for more information regarding this program.
Doctor Walter J. Curran, Jr. Receives ACR Gold Medal at the College's 2016 Annual Meeting
NRG Oncology Group Chair, Walter J. Curran, Jr., MD, FACR, was one of three radiology professionals to be awarded a Gold Medal from the American College of Radiology (ACR) at the college’s annual meeting on May 15, 2016. The ACR Gold Medal, awarded by the Board of Chancellors, recognizes individuals that have displayed exceptional, professional contributions to the ACR and to the discipline of radiology. Dr. Curran received this award for his numerous accomplishments within the radiation oncology community, and most especially with the Radiation Therapy Oncology Group (RTOG) and NRG Oncology. Prior to the formation of NRG Oncology in 2014, he served as the RTOG Group Chair from 1997 and is currently the Chairman of the Board of Directors for the RTOG Foundation.

Doctor Norman Wolmark Nominated for Giants of Cancer Care® Award
Norman Wolmark, MD, an NRG Oncology Group Chair, has been selected by his peers as a nominee in OncLive's 2016 Giants of Cancer Care® awards for recognition of his contributions in breast cancer research. The nominees from each category were announced on June 2, 2016 at OncLive's gala event, "An Evening Under the Stars," at the Adler Planetarium in Chicago and the winners will be announced at the PER® 34th Annual Chemotherapy Foundation Symposium in New York City in November 2016. Read more about OncLive's Giants of Cancer Care® awards: http://giants.onclive.com/

Drs. Wolmark and Geyer invited speakers at inaugural breast cancer meeting in China
Norman Wolmark, MD, an NRG Oncology Group Chair, and Charles E. Geyer, Jr., MD, Associate Director for Clinical Research at Virginia Commonwealth University Massey Cancer Center, were invited speakers at the inaugural Guangzhou Breast Cancer Symposium held in Guangzhou, China on June 17-18. Dr. Wolmark gave two presentations, "Contributions of NSABP over 50 years: An odyssey of breast clinical trials" and "Introduction of the framework of NSABP." Dr. Geyer's presentation was titled, "Is neoadjuvant systemic therapy the standard of care for stage II HER2+ breast cancer: MD Anderson Cancer Center approach for treating Stage II breast cancer?" Dr. Geyer also presented highlights from the 2016 ASCO annual meeting. The symposium, which was attended by more than 500 expert medical oncologists and surgeons from China and featured speakers from the United States and Great Britain, was organized by Ning Liao, MD, a leading breast cancer researcher and head of the Breast Department, Cancer Center at Guangdong General Hospital in Guangzhou, China.

Thomas George, MD, FACP, Named Chair of the NRG Oncology Colorectal Cancer Committee
Dr. Thomas J. George, Jr., Director of the Gastrointestinal Oncology Program at the University of Florida and Director of the UF Health Cancer Center Joint Oncology Research Program, has been named chair of the NRG Oncology Colorectal Cancer Committee. Dr. George has been a member of the NRG Oncology Gastrointestinal Cancer Committee and its core committees since their inception.

NRG Oncology would like to thank Carmen J. Allegra, MD, for serving as the previous Gastrointestinal Cancer Committee Chair. Allegra, who is the chief of the Division of Hematology and Oncology in the College of Medicine at the University of Florida in Gainesville and editor-in-chief of the Journal of the National Cancer Institute, also served as NRG Oncology Deputy Chair, chair of the Communications Committee, and co-chair of the Publications Committee. As NRG Oncology Deputy Chair, Dr. Allegra was a member of the Board of Directors, and a member of the Executive Committee of the Board. He also served on the Research Strategy Committee. Dr. Allegra will continue his position in the NSABP Foundation.

Thomas B. Julian, MD, named chair of NRG Oncology Communications Committee; co-chair of NRG Oncology Publications Committee
We are pleased to announce that Dr. Norman Wolmark has designated Dr. Thomas Julian as an NRG Oncology deputy chair, and appointed him chair of the NRG Oncology Communications Committee and co-chair of the NRG Oncology Publications Committee. He is currently the chair for the NRG Surgical Oncology Committee and a co-chair for the NRG Local – Regional Breast Subcommittee. Dr. Julian is director of the Division of Breast Surgical Oncology at Allegheny General Hospital, part of Allegheny Health Network in Pittsburgh, Professor of Surgery at Drexel University College of Medicine, and Professor of Surgery at Temple University School of Medicine. He is an accomplished breast cancer surgeon, researcher and educator, and is senior director of Medical Affairs at NSABP Foundation.
NRG Oncology Gastrointestinal Cancer Committee (continued from page 1)

NRG Oncology Colorectal Cancer Committee.

The NRG-GI002 trial, planned for activation in Fall 2016, is representative of this multidisciplinary treatment mantra. Nicknamed “TNT” (for Total Neoadjuvant Therapy), this study is a modular phase II master protocol that allows multiple hypotheses to be tested simultaneously leveraging a consistent control arm to optimize trial efficiencies. “By bringing all systemic and local therapies into the pre-operative space, we are able to ensure all patients receive optimal multimodality therapy and can isolate the individual variables we desire to test, ultimately getting answers faster for our patients,” Dr. George states. The trial will utilize a novel surrogate endpoint developed and validated by Dr. Greg Yothers, the NAR (Neoadjuvant Rectal) Score. The study will open with the first experimental arm assessing the impact of a novel radiosensitizer, veliparib (a PARP inhibitor) on tumor downstaging in locally advanced disease. Several additional concepts have been developed by Colorectal Cancer Committee members, approved by NRG Oncology leadership and are moving through the regulatory processes to be opened as independent arms through protocol amendments.

For metastatic disease, personalized and targeted treatments remain a patient priority. “Colorectal cancer is increasingly recognized as a group of unique diseases which have unique vulnerabilities. We can’t continue to treat everyone the same,” says Dr. George. While we await the results of the recently completed BRAF-mutated study (PI – S. Kopetz) utilizing irinotecan and cetuximab with or without vemurafenib, it is clear that small subsets of mutationally profiled patient tumors can be successfully identified and recruited to studies across the NCTN groups. Additional upcoming studies of interest involve targeting HER2 overexpressing colorectal cancer. The recently completed PD-1 inhibitor study in MSI-H colorectal cancer, conducted by several NRG Oncology Colorectal Cancer Committee members, demonstrates that immune therapy can benefit patients. “We are incredibly optimistic that targeted and immune therapies can benefit patients with colorectal cancer, particularly now that we have more clear means to identify and treat subsets of appropriate patients,” Dr. George concluded.

For the Non-Colorectal Cancer Committee, RTOG trials are leading a cultural change through the discovery and validation of predictive markers. “The discovery of predictive markers, promising targets, and effective targeted agents has lagged behind in pancreatic cancer for one fundamental reason: the lack of adequate tissue specimens collected in clinical trials from patients with locally advanced and metastatic disease. Most cases of pancreatic cancer are diagnosed with fine-needle aspirate (FNA) specimens that contain barely enough cells to make a cytologic diagnosis, let alone to evaluate molecular predictors that can inform treatment decisions,” says Dr. Crane. Translational studies from RTOG 9704 identified the relevance of human Equilibrative Nucleoside Transporter 1 (hENT1) as a predictor of gemcitabine activity. Those efforts have led to the LEAP (Low hENT1 and Adenocarcinoma of the Pancreas) trial, the first trial to use an integral biomarker in pancreatic cancer. Patients with low hENT1 expressing metastatic pancreatic cancer determined by immunohistochemistry were randomized to gemcitabine versus C0-101, lipid conjugated form of gemcitabine that enters the cell independent of hENT1. The LEAP trial has completed accrual and survival results are expected this year.

Additionally, a phase II study from Princess Margaret, MGH and MDACC have shown that high dose per fraction of radiation to primary liver tumors can be delivered safely and lead to local tumor control over 90 percent. Those trials have led to RTOG 1112 in hepatocellular carcinoma (HCC) and the proposed NRG-GI001 in intrahepatic cholangiocarcinoma. Both of these trials have a randomized phase II/III design comparing high dose per fraction radiation with systemic therapy. Since there is no standard of care for these indications, SBRT and hypofractionated radiation may lead to a significant survival benefit, and a change in the standard of care.

Let Us Know How We Are Doing!

The NRG Oncology Communications Committee wants to hear your opinions and ideas. We are looking for feedback regarding the frequency and the content you are receiving from us through our newsletter, website, Twitter page, and more.

Please take our survey and let us know what types of topics you would like to see included in our communications at NRG Oncology!