NRG Cancer Prevention and Control Meeting

Lisa Kachnic, MD, Cancer Control Chair
Warner Huh, MD, Prevention Chair
Debra Barton, PhD, Cancer Control Vice-Chair
Julie Bauman, MD, Prevention Vice-Chair

July 22, 2021
NRG Oncology NCORP Org Chart

NRG Executive Committee
NCORP PIs: Deb Bruner (contact PI) & Joan Walker
Assoc. Chair: Lisa Kachnic
NRG Group Chairs, NCORP Comm Chairs, NCORP Stats

NRG NCORP Steering Committee
NCORP PIs, Comm Chairs/Vice Chairs, Stats, Community MDs,
New Investigator Liaisons, PT Advocates, Admin

- Ca Prevention and Control Research (CPCR)
  Co-Chairs:
  L Kachnic, W. Huh
  Vice Chairs:
  D Barton, J Bauman
  - Neurocognitive Function
  - Gender-specific Symptom Mgmt
  - Radiation Alterations
  - Behavioral Modifications
  - Ca Risk Reduction

- Cancer Care Delivery Research (CCDR)
  Chair: M Cooley
  Vice Chair: M Hudson
  - Ca Survivorship
  - Implement EBP in Symptom Mgmt

- Health Disparities Research (HDR)
  Chair: J. Wenzel
  Vice Chair: C Hughes
  - Racial/Ethnic Minorities
  - Elderly
  - Rural Populations

- Patient Centered Outcomes Research (PCOR)
  Chair: B. Movsas/
  Vice Chairs
  L. Wenzel, P Ganz
  - PROs tx trials
  - Consult on PROs in CCC, CPC, CCD, HDC trials

NRG NCORP Operations Committee

NRG NCORP Finance Committee
NRG NCORP Cancer Prevention and Control Priorities

- Improvement or delay in decline of neurocognitive function
- Reducing of gender-specific symptoms including lymphedema and sexual function
- Testing therapeutic delivery modifications to improve QoL and cost-effectiveness in localized cancers while maintaining efficacy
- Reducing cancer risk through optimal screening, biomarker evaluation and risk reduction strategies and
- Assessing behavioral interventions to decrease cancer risk and mitigate cancer treatment-related symptoms
Announcements
NCORP Spotlight

NRG will begin highlighting one NCORP site each month in the NRG newsletter. If you’d like your NCORP site to participate please contact Erica Field, fielde@nrgoncology.org
Welcome Dr. Huh!

Warner Huh, MD, Chair of the Department of Obstetrics and Gynecology at the University of Alabama at Birmingham (UAB), appointed new chair of the NRG Oncology Cancer Prevention Committee efforts.
CPC Trials
## Opened NRG CPC Trials

**accrual as of June 30, 2021**

<table>
<thead>
<tr>
<th>Study No</th>
<th>Disease Site</th>
<th>Description</th>
<th>Date Activated</th>
<th>Target Accrual</th>
<th>Total Accrual</th>
<th>NCORP Accrual (%)</th>
<th>Expected Closure Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 0278</td>
<td>Cervix</td>
<td>Physical function/QoL before and after non-radical surgical therapy for stage IA1 (LVSI+) and IA2-IB1 (=2CM) cervical cancer</td>
<td>10/1/12</td>
<td>220</td>
<td>217</td>
<td>&lt;1%</td>
<td>December 2021</td>
</tr>
<tr>
<td>NRG CC003</td>
<td>Lung</td>
<td>Seamless phase II/III PCI vs. PCI with hippocampal sparing for cognitive fx preservation in small cell lung cancer</td>
<td>12/7/15</td>
<td>172 (II)</td>
<td>176 (II)</td>
<td>30%</td>
<td>February 2022</td>
</tr>
<tr>
<td>Study No</td>
<td>Disease Site</td>
<td>Description</td>
<td>Date Activated</td>
<td>Target Accrual</td>
<td>Total Accrual</td>
<td>NCORP Accrual (%)</td>
<td>Expected Closure Date</td>
</tr>
<tr>
<td>----------</td>
<td>--------------</td>
<td>-------------</td>
<td>----------------</td>
<td>----------------</td>
<td>--------------</td>
<td>------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>NRG CC005</td>
<td>GI</td>
<td>FORTE/Five or Ten Year</td>
<td>Activating late July</td>
<td>9,500</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRG CC008</td>
<td>Ovarian</td>
<td>Non-rand. prospective trial comparing non-inferiority of Salpingectomy to salpingo-Oophorectomy to Reduce risk of Ovarian Ca among BRCA1 carriers (SOROCk)</td>
<td>6/23/2020</td>
<td>2262</td>
<td>50</td>
<td>13%</td>
<td>March 2031</td>
</tr>
<tr>
<td>NRG CC009</td>
<td>Lung</td>
<td>SRS vs. HA-WBRT for 10 or Fewer Brain Metastases from SCLC</td>
<td>2/24/2021</td>
<td>200</td>
<td>2</td>
<td>100%</td>
<td>August 2024</td>
</tr>
</tbody>
</table>
Women with IA1-IB1 (≤2cm) carcinoma of the cervix who have been consented for surgery will be approached for study participation. Pre-entry cone biopsy/LEEP (depth of invasion ≤ 10mm)

Study Entry

Pre-operative QOL Study Survey

Fertility Preservation Group:
Conization with pelvic lymphadenectomy (If the lateral margins were positive on the first cone biopsy/LEEP, patients must have a second cone biopsy/LEEP at the time of the pelvic lymphadenectomy)

No Wish for Future Fertility Group:
Simple hysterectomy with pelvic lymphadenectomy (If the lateral margins were positive on the first cone biopsy/LEEP, patients must have a second cone biopsy/LEEP prior to hysterectomy)

If depth of invasion (sum of the pre and post entry biopsies) is ≤10 mm, only ECC is required.

If any of the following criteria are met, patient will be followed for survival only:
- Depth of invasion (sum of the pre and post entry biopsies) is >10 mm
- Positive pelvic lymph nodes on final pathology
- Adjuvant therapy required

Post-Operative
Follow-up Visits 4-6 weeks Post-op and every 3 months (3, 6, 9, 12) for 1 year then every 6 months (18, 24, 30, 36) for 2 years and QOL Study Surveys 4-6 weeks Post-Op and every 6 months (6, 12, 18, 24) for two years
NRG CC003: Phase IIR/III Trial Prophylactic Cranial Irradiation with or without Hippocampal Avoidance for Small Cell Lung Cancer

PIs: Minesh Mehta (Miami Cancer Institute) + Vinai Gondi (Northwestern)

**Basic Eligibility:** Small cell lung cancer; PR or CR to chemo; ECOG PS ≤ 70; MRI scan

**Small Cell Lung Ca** → **Stratify**

- **Stage**
- **Age**
- **Concomitant Memantine**

**Randomize**

- PCI 25Gy/10
- HA-PCI 25Gy/10

**Sample Size:** Phase IIR: 172 patients; Phase III: 392 patients

**Primary endpts:**
- Phase IIR—Intracranial relapse rate at 12 months
- Phase III—HVLT-R delayed recall deterioration at 6 months

**Statistical Design:**
- Phase IIR: Non-inferiority margin of >20% difference. 164 analyzable pts.
- Phase III: 29% with PCI vs. 14.5% with HA-PCI. 196 analyzable pts
NRG-CC005/FORTE

PI: Robert Schoen, MD

Sample size = 9500

Biospecimen collection:
• Streck tube (1)
• Stool sample (3)
• FFPE tissue

NRG-CC005 SCHEMA

Participants ≥ 50 and < 70 years with First Diagnosis of 1-2 Non-Advanced Adenomas within Prior 4 years

STRATIFICATION
• Age (50-55, 56 - < 70)
• Gender (Female, Male)
• Time from Qualifying Colonoscopy to Randomization (< 2 years, 2-4 years)

RANDOMIZATION*

Arm 1
5-Year and 10-Year Surveillance Colonoscopy after Qualifying Colonoscopy

Arm 2
10-Year Surveillance Colonoscopy after Qualifying Colonoscopy

* Randomization is 1:1.
NRG-CC008

Co-PIs: Joan Walker, MD; Warner Huh, MD; Kathryn Pennington, MD

Sample size = 2262

Primary objective: To compare the non-inferiority BLS with delayed oophorectomy to BSO to reduce the risk of ovarian cancer among women with deleterious BRCA1 germline mutations
NRG CC009: Phase III Trial Stereotactic Radiosurgery versus Hippocampal-Avoidant Whole-Brain Radiotherapy for 10 or Fewer Brain Metastases from Small Cell Lung Cancer

PIs: Chad Rusthoven (Univ of Colorado) + Vinai Gondi (Northwestern)

Sample Size: 200 patients

**Basic Eligibility:** Small cell lung cancer; ≤10 brain mets ≤3cm; total vol 30cc; KPS ≥70

**Brain Mets from Small Cell Lung Ca**

**S**tratify

**DS-GPA Exposure to NCF Testing***

*S pts enrolled on SWOG trial will have been exposed to NCF Testing

**R**andomize

- SRS alone
- HA-WBRT 30 Gy/10

**Primary endpt:** Time to cognitive failure--HVLT-R, COWA, and TMT A and B

**Basic Statistical Design:** Cognitive fxn failure 58.8% at 6 mos with HA-WBRT+mem vs. 41.8% at 6 mos with SRS. 150 analyzable pts
Questions
<table>
<thead>
<tr>
<th>Study</th>
<th>Protocol Title</th>
<th>Accrual (6/30/121)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1820</td>
<td>Testing Diet Intervention vs. Non-Diet Intervention for Management of Bowel Symptoms in Rectal Cancer Survivors (PI Sun)</td>
<td>63/126</td>
<td>Tracy Crane is the NRG Study Champion; NRG has enrolled 17 participants</td>
</tr>
<tr>
<td>S0820</td>
<td>Double Blind Placebo-Controlled Trial to Prevent Recurrence of High-Risk Adenomas and Second Primary Colorectal Cancers (PACES) (PI Zell)</td>
<td>316/491</td>
<td>Jenny Dorth is the NRG Study Champion; NRG has enrolled 35 participants</td>
</tr>
<tr>
<td>EA1151</td>
<td>Tomosynthesis Mammographic Imaging Screening Trial (TMIST) (PI Pisano)</td>
<td>49,860/164,946</td>
<td>NRG enrolled 3,363 participants</td>
</tr>
<tr>
<td>A221805</td>
<td>Duloxetine To Prevent Oxaliplatin-Induced CIPN: Rand. Double-Bind, Placebo-Controlled Phase II To Phase III Study (PI Smith)</td>
<td>59/327</td>
<td>Jordan Kharofa is the NRG Study Champion; NRG has enrolled 7 participants</td>
</tr>
<tr>
<td>EA2185</td>
<td>Comparing the Clinical Impact of Pancreatic Cyst Surveillance Programs</td>
<td>62/4606</td>
<td>Aasma Shaukat is the NRG Study Champion; NRG has enrolled 8 participants</td>
</tr>
</tbody>
</table>
SWOG 1820: Testing Diet Intervention vs. Non-Diet Intervention for Management of Bowel Symptoms in Rectal Cancer Survivors

Rectal cancer survivors (N=94, 47 per arm)
- Between 6-24 months post-treatment completion
- Low anterior resection syndrome (LARS) score of 21-42 (minor/major symptoms)
- English-speaking
- 18 years and older

**Intervention Arm (AIMS-RC)**
- 10 telephone coaching calls over 4 months (about 20-40 minutes)
  - Goal setting
  - Identifying and overcoming challenges
  - Food and symptom diary
  - Motivational interviewing and problem-solving (MAPS)
- AIMS-RC resource manual
- Personalized text/email messaging support between calls

**Attention Control Arm (Healthy Living Education)**
- 10 telephone calls over 4 months (about 20-40 minutes)
  - Sleep, sun safety, food safety, skin care, active wear, bone health, physical activity, clinical trials, evaluating online resources, screening & surveillance
- Attention control resource manual
- Automated, standard text/email messaging support between calls

**Outcomes:**
- Bowel Function (MSKCC-BFI)
- QOL (COH-QOL-CRC), LARS score, self-efficacy (PROMIS), motivation, positive/negative affect (PANAS), diet quality, feasibility and acceptability

2-3 weeks by telephone: 24 hour dietary recall, 3 day food and symptom diary

*Centrally-administered by trained health coaches at the University of Arizona
SWOG 0820: Double Blind Placebo-Controlled Trial to Prevent Recurrence of High Risk Adenomas and Second Primary Colorectal Cancers (PACES)

**Inclusion:**
- Stage 0-III colorectal adenocarcinoma
- s/p partial colectomy, polypectomy, TAE +/- chemo(RT)
- Register 6 mo - 15 mo postop, ≥30 d post chemo(RT)
- NED at colonoscopy +/- CT scan ≥ 6 mo postop

**Exclusion:**
- No high CV risk
- No hearing loss
- No high-dose NSAID
- No GI ulcer
- No family hx FAP, HNPCC, IBD

*Stratify by stage/adjuvant tx

**Randomize**
- Placebo X 3y
- Eflornithine 500mg/d + Sulindac 150mg/d X 3y

**Year 3**
- Colonoscopy
- Audiogram
- 1° endpoint = 3y event rate high-risk adenomas + 2nd primary CRCs
- Stats: 80% power for event rate 27% → 13.5%

**Year 8**
- Colonoscopy at years 3 and 8
- F/U schedule: q3mo X 1y → q6mo X 2y → q1y X 5y

**F/U schedule:**
- Colonoscopy at years 3 and 8

**FOLLOW-UP**
EA1151 - TMIST

**TMIST Cohort**
Women Ages 45-74 Presenting for Breast Screening

**Randomization**

- Digital Mammography (DM)
  - Annual DM Screening¹ (Baseline, 12-, 24-, 36-, 48-Months, or Until Cancer Detected)
  - Biennial DM Screening²

- Tomosynthesis (TM)
  - Annual TM Screening¹ (Baseline 12-, 24-, 36-, 48-Months, or Until Cancer Detected)
  - Biennial TM Screening² (Baseline, 24-, 48-Months or Until Cancer Detected)

**Clinical Follow-Up**

**Long-Term Follow-Up**
A221805

Schema Phase II

$N = 177$

- 3-arm
- Double-blind
- Placebo-controlled
- Stratification
  - Male / Female
  - CAPOX / FOLFOX

Registration

Randomization

Duloxetine 30mg

Duloxetine 60mg

Placebo

Schema Phase III:
If duloxetine is shown to be clinically active

$N = 150$

Registration

Randomization

Most promising dose of duloxetine

Placebo

- 2-arm
- Double-blind
- Placebo-controlled
- Stratification
  - Male / Female
  - CAPOX / FOLFOXm

Registration

Randomization

Duloxetine 30mg

Duloxetine 60mg

Placebo
EA2185

**Schema**

**Randomization**

- **Arm A**
  - Low Intensity Surveillance
  - Long-term Follow-up

- **Arm B**
  - High Intensity Surveillance
  - Long-term Follow-up

Asymptomatic patients aged 50-75 with ≥ 1cm pancreatic cyst

Accrual: \( n = 4606 \)
## Developing NRG NCORP Trials

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Disease</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRG-CC2047 (concept)</td>
<td>Gynecologic Cancer Therapy: The Vaginal Microbiome and Patient Symptom Experience</td>
<td>R01 submitted July 2021</td>
</tr>
<tr>
<td>NRG-CC2046 (concept)</td>
<td>Impact of Sentinel Lymph Node Mapping on Patient Reported Lower Extremity Limb Dysfunction in Endometrial Cancer</td>
<td>Pending final DCP review</td>
</tr>
</tbody>
</table>
## Concepts in Development

<table>
<thead>
<tr>
<th>Concept</th>
<th>Disease</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rand., Blinded, Placebo Controlled Phase 2 Trial of Concurrent ChemoRT w/ and w/out the BMX-001 in Patients with H&amp;N Cancer</td>
<td>Head &amp; Neck</td>
<td></td>
</tr>
<tr>
<td>Endometrial cancer prevention in women with obesity with the levonorgestrel-releasing intrauterine system</td>
<td>Gyn/Endometrial</td>
<td>Developed from pre-LOI from</td>
</tr>
<tr>
<td>Stereotactic Pelvic Radiotherapy in Uterine Cancers (SPARTACUS) III</td>
<td>Uterine</td>
<td></td>
</tr>
<tr>
<td>Ph III trial to evaluate limb cryoocompression for prevention of paclitaxel-induced peripheral neuropathy</td>
<td>Breast &amp; Gyn</td>
<td>Collaborative NCORP RB concept</td>
</tr>
<tr>
<td>Preoperative RT to Improve Cosmetic Outcomes in Breast Ca Pts</td>
<td>Breast</td>
<td></td>
</tr>
</tbody>
</table>
Resources for Concept Development

• NRG NCORP Website
  ➢ https://www.nrgoncology.org/Scientific-Program/NRG-NCORP-Research-Base
  ➢ Slide Deck Orientation: Click link under “Learn more about opportunities and working with NRG NCORP”

• CPC Concept Development Form

• CPC Pre-LOI Form
  ➢ Contact Erica Field, fielde@nrgoncology.org
NCORP CPC Contact Information

Cancer Control and Symptom Management
Chair: Lisa Kachnic, MD, FASTRO;
lak2187@cumc.columbia.edu
Vice-Chair: Debra Barton, PhD;
debbartn@med.umich.edu

Cancer Prevention
Chair: Warner Huh, MD
whuh@uabmc.edu
Vice-Chair: Julie Bauman, MD;
jebaum@arizona.edu

Budgets/Other NCORP Questions
Erica Field, NCORP Administrator;
fielde@nrgoncology.org
One year follow up of NRG Oncology CC001

Sunjay Shah, MD
Department of Radiation Oncology
Helen F. Graham Cancer and Research Center
Christiana Care Health System
NRG-CC001: Phase III Trial Memantine and WBRT with or without Hippocampal Avoidance in Patients with Brain Metastases

One year follow up of NRG Oncology CC001

Sunjay Shah, MD
Department of Radiation Oncology
Helen F. Graham Cancer and Research Center
Christiana Care Health System
Newark, DE
Helen F. Graham Cancer Center & Research Institute
Cancer Research
Serving Delaware, Pennsylvania, New Jersey and Maryland

- Newark Campus
- Wilmington Campus
- Concord Campus
- Beebe Health
- Beebe Health - South Coastal Campus
- Cecil County Campus - added Jan 2020

*Data in this presentation does not reflect the addition of Union Hospital and affiliates except where noted.*
Brain mets are a major clinical problem

- Patients with brain metastases are a common clinical problem. 30-40% of lung cancer patients will develop brain metastases at some point.
- Patients present with severe neurological deficits. Chemotherapy has poor efficacy due to the blood/brain barrier.
Whole-Brain Radiation Therapy (WBRT)

- Logistically simple
- Little change in technique over decades
- Toxicity of WBRT (cognitive)
  - Need to decrease toxicity to improve therapeutic ratio of WBRT

Wang JAMA Onc 2018
The trial has a strong and appealing scientific rationale

• Previous clinical trials had demonstrated a specific early decrease in short term memory in patients receiving whole brain XRT as opposed to executive and fine motor function.

• The hippocampi are the key parts of the limbic system involved with forming episodic and spatial memories. They are located in the medial temporal lobes of the brain.
Hippocampus
Pathophysiology

- Hippocampus primary site adult neurogenesis
  - Critical for learning and memory

- Hippocampus most sensitive to RT injury

Monje, Curr Op Neuro 2003; Laack, Sem Rad Onc, 2004
Hippocampal Physiology

- Generation of new hippocampal neurons arises from neural stem cells located in the subgranular layer of the hippocampus.
- Hippocampal neurogenesis vital to memory-related function
- 97% reduction in new neurons 2 months after cranial RT

Gondi V, Torne WA, M Mehta, Radiother Oncol 2010
Monje, M et al. Nat Med 2002;8(9) 955-962
Anatomy of the Hippocampus

Red: Hippocampus
Green: Hippocampal Avoidance Zone
Conformal Avoidance Hippocampal Neural Stem Cells

Hippocampal avoidance WBRT (HA-WBRT)
- 30 Gy
- 8 Gy

Conventional WBRT
- 30 Gy

NRG ONCOLOGY™
RTOG 0933

- Single-arm phase II trial of HA-WBRT (30 Gy in 10 fractions)
  - Credentialing and central review of hippocampal contouring and IMRT planning

- Mean decline in HVLT-Delayed Recall from baseline to 4 months: 7.0% (95% CI: -4.7-18.7%)
  - Significantly less compared to historical control: 30% ($p=0.0003$)

Need phase III data for level I evidence

Gondi et al. JCO 2014
NRG-CC001: Phase III Trial Memantine and WBRT with or without Hippocampal Avoidance in Patients with Brain Metastases

Basic Eligibility: Brain metastases 5mm outside hippocampus; KPS≥70; 3D MRI scan; hydrocephalus/ventricular distortion excluded; baseline NCF testing

Brain Metastasis

Stratify

RPA
Prior Therapy

Randomize

WBRT 30Gy + Memantine

HA-WBRT 30Gy + Memantine
Baseline Characteristics

518 randomized patients

<table>
<thead>
<tr>
<th>Baseline</th>
<th>WBRT+Mem n=257</th>
<th>HA-WBRT+Mem n=261</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median 61</td>
<td>Median 62</td>
<td>0.66</td>
</tr>
<tr>
<td>RPA class</td>
<td>Class I: 14.8%</td>
<td>Class I: 12.6%</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>Class II: 85.2%</td>
<td>Class II: 87.4%</td>
<td></td>
</tr>
<tr>
<td>Neurologic symptoms</td>
<td>None: 46.3%</td>
<td>None: 43.3%</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>Minor: 33.5%</td>
<td>Minor: 35.2%</td>
<td></td>
</tr>
<tr>
<td>Primary tumor</td>
<td>Lung 58.8%</td>
<td>Lung 59.8%</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>Breast 17.5%</td>
<td>Breast 19.5%</td>
<td></td>
</tr>
<tr>
<td>KPS</td>
<td>70: 20.6%</td>
<td>70: 18.4%</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>80: 29.2%</td>
<td>80: 31.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>90-100: 50.2%</td>
<td>90-100: 50.6%</td>
<td></td>
</tr>
</tbody>
</table>

No differences in baseline patient characteristics, including cognitive function and patient-reported symptom burden
Primary Endpoint

- Hippocampal avoidance prevents cognitive function failure
  - Hazard ratio = 0.756  \( p = 0.029 \)
  - Separation of the curves starting at 3 months and maintained through the follow-up period

Median follow-up for alive patients: 12.1 months
Cognition Domains at 6 Months

- Hippocampal avoidance reduces deterioration of
  - 4 months: Executive function (Trail Making Test B)
  - 6 months: Learning and memory (HVLT-R Recognition)

### Deterioration at 6 months:

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>WBRT +Mem n=77</th>
<th>HA-WBRT +Mem n=61</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVLT-R Total Recall</td>
<td>26.8%</td>
<td>14.7%</td>
<td>0.07</td>
</tr>
<tr>
<td>HVLT-R Delayed Recall</td>
<td>30.0%</td>
<td>20.6%</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>HVLT-R Recognition</strong></td>
<td><strong>36.3%</strong></td>
<td><strong>17.6%</strong></td>
<td><strong>0.011</strong></td>
</tr>
<tr>
<td>Trail Making Test Part A</td>
<td>28.0%</td>
<td>17.6%</td>
<td>0.13</td>
</tr>
<tr>
<td>Trail Making Test Part B</td>
<td>35.9%</td>
<td>23.9%</td>
<td>0.12</td>
</tr>
<tr>
<td>Controlled Oral Word Association</td>
<td>6.2%</td>
<td>11.8%</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Median follow-up for alive patients: **12.1 months**
Cognition Domains Over Time

- Hippocampal avoidance reduces deterioration of
  - 4 months: Executive function (Trail Making Test B)
  - 6 months: Learning and memory (HVLT-R Recognition)

- Hippocampal avoidance preserves all learning and memory domains over time
  - HVLT-R total recall, delayed recall and recognition

Mixed effects models using multiple imputation:

Higher score indicates better performance

Median follow-up for alive patients: 12.1 months
Patient-Reported Outcomes

- Hippocampal avoidance preserves patient-reported symptoms at 6 months:
  - Neurologic symptom burden
  - Interference of neurologic symptoms in daily activities

- Hippocampal avoidance preserves patient-reported cognitive factor over time:
  - Hippocampal avoidance associated with less problems remembering things at 6 months ($p=0.016$)

Mixed effects models using multiple imputation: $p=0.0425$

Median follow-up for alive patients: **12.1 months**
## Survival

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>WBRT+Mem n=257</th>
<th>HA-WBRT+Mem n=261</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial Progression-Free Survival</td>
<td>Median: 5.3 months 95% CI: 4.7-6.0</td>
<td>Median: 5.0 months 95% CI: 4.4-6.2</td>
<td><strong>0.076</strong></td>
</tr>
<tr>
<td></td>
<td>HR = 1.20 95% CI: 0.98-1.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Survival</td>
<td>Median: 7.6 months 95% CI: 5.8-10.1</td>
<td>Median: 6.3 months 95% CI: 4.0-7.7</td>
<td><strong>0.242</strong></td>
</tr>
<tr>
<td></td>
<td>HR = 1.14 95% CI: 0.91-1.43</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No significant differences in intracranial PFS or overall survival

HA region relapses:

**HA-WBRT+Mem 11**  **WBRT+Mem 17**

Median follow-up for alive patients: **12.1 months**
NRG CC001: Conclusions

- Hippocampal sparing during WBRT plus memantine for brain metastases preserves cognitive function and patient-reported symptoms

- Similar toxicity, **intracranial PFS and overall survival** outcomes
- Benefits in executive functioning at 4 mos and learning and memory at 6 mos
- Better patient-reported cognition, symptom interference, fatigue, difficulty speaking, and problems remembering things at 6 months
Conclusions

For brain metastasis patients eligible to receive WBRT and whose survival is expected to be 4 months or longer, hippocampal avoidance using IMRT should be considered standard of care.
NRG CC001 Accrual

Thank you

Accrual

Projected Accrual

Accrual: 16 pts/month. Completed 2 years earlier than projected.

Community's interest in developing safer approaches to deliver WBRT.

NRG ONCOLOGY™
CCTG CE.7: Phase III Trial Stereotactic Radiosurgery versus Hippocampal Avoidant WBRT+memantine for 5-15 Brain Metastases

Basic Eligibility: 5-15 brain mets; largest met <2.5cm; total brain met vol ≤30cc

5-15 Brain Metastases

- DS-GPA
- Targeted/Immunotx
- SRS System
- Histology

Randomize

- HA-WBRT + Memantine
- SRS

Sample Size 206

Co-primary endpoints:
- Overall survival
- Neurocog-progression free survival
RTOG 1203

Ann Klopp, MD, PhD
Associate Professor
Director of Radiation Oncology Gynecological Services
Center Medical Director, COVID Vaccine Clinic
The University of Texas MD Anderson Cancer Center
IMRT improves late toxicity compared to conventional RT: An update on NRG Oncology-RTOG 1203

Anamaria Yeung, MD, Stephanie Pugh, PhD, Ann Klopp, MD, PhD, Karen Gil, PhD, Lari Wenzel, PhD, Shannon N. Westin, MD, MPH, Andre Konski, MD, MBA, MA, FACR, J. Spencer Thompson, MD, Desiree E. Doncals, MD, Guilherme H.C. Cantuaria, MD, David P. D’Souza, MD, Amy Chang, MD, Vijayananda Kundapur, MD, Dasarahally S. Mohan, MD, Michael L. Haas, MD, Yong Bae Kim, MD, Catherine L. Ferguson, MD, Lisa A. Kachnic, MD, Deborah Bruner, PhD

ASTRO 2019
September 17, 2019
Disclosures

• I have no disclosures to report.
Eligibility
Women with endometrial or cervical cancer requiring post-operative pelvic radiation or chemoradiation

Stratification factors
- RT dose
  - 45 Gy
  - 50.4 Gy
- Chemotherapy
  - No Chemotherapy
  - 5 cycles of weekly cisplatin at 40mg/m²
- Disease Site
  - Endometrial
  - Cervix

Sample size:
279 patients

Phase III randomized trial

NRG Oncology RTOG 1203

IMRT pelvic radiation treatment

4-field pelvic radiation treatment
Objectives

Primary Objective:
• To determine if **acute GI toxicity** is reduced with IMRT in week 5 of RT using patient reported measure of toxicity (EPIC Bowel)

Secondary Objectives:
• Acute urinary toxicity (EPIC tool)
• Quality of life (FACT-G)
• **LRC, DFS, OS**
• Validate EPIC in women
• Health utilities analysis

---

Median f/u for all patients: 37.8 months

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before RT</td>
<td>Baseline</td>
</tr>
<tr>
<td>3 weeks after RT start</td>
<td>Compare early acute toxicity</td>
</tr>
<tr>
<td>End of RT (5 weeks after RT start)</td>
<td>Maximum difference in acute toxicity</td>
</tr>
<tr>
<td>4-6 weeks after RT</td>
<td>Compare resolution of acute toxicity</td>
</tr>
<tr>
<td>1 year from the start of RT</td>
<td>Early chronic toxicity</td>
</tr>
<tr>
<td>3 years from the start of RT</td>
<td>Long term toxicity</td>
</tr>
</tbody>
</table>
Disease Outcomes

- There were no differences between arms.

<table>
<thead>
<tr>
<th></th>
<th>2yr LRF</th>
<th>2yr DFS</th>
<th>2yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRT</td>
<td>2.6%</td>
<td>89.1%</td>
<td>95.1%</td>
</tr>
<tr>
<td>4 Field</td>
<td>1.4%</td>
<td>86.1%</td>
<td>99.3%</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.82 (0.20, 3.27)</td>
<td>1.39 (0.82, 2.35)</td>
<td>0.76 (0.32, 1.79)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.81 (Gray’s test)</td>
<td>0.21 (log-rank)</td>
<td>0.53 (log-rank)</td>
</tr>
</tbody>
</table>
Results: Mean Rectum Doses by Treatment

Error bars represent 95% confidence interval
Results: Mean Bowel Dose by Treatment

Error bars represent 95% confidence interval.
Patient-Reported Bowel Toxicity (EPIC)

<table>
<thead>
<tr>
<th></th>
<th>Week 3 of RT</th>
<th>Week 5 of RT</th>
<th>4-6 Weeks Post-RT</th>
<th>1 Year Post-RT</th>
<th>3 Years Post-RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRT</td>
<td>114</td>
<td>111</td>
<td>106</td>
<td>98</td>
<td>68</td>
</tr>
<tr>
<td>4Field</td>
<td>134</td>
<td>130</td>
<td>131</td>
<td>114</td>
<td>79</td>
</tr>
</tbody>
</table>

* p < 0.05
Patient-Reported Diarrhea (PRO-CTCAE)

**PRO-CTCAE score 3+ Diarrhea Frequency**

- IMRT vs. 4Field
- Statistical significance: *p < 0.05

**PRO-CTCAE Anti-diarrheal medication 2+ times daily**

- IMRT vs. 4Field
- Statistical significance: *p < 0.05

<table>
<thead>
<tr>
<th></th>
<th>Week 5 of RT</th>
<th>4-6 Weeks Post-RT</th>
<th>1 Year Post-RT</th>
<th>3 Years Post-RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRT</td>
<td>92</td>
<td>88</td>
<td>87</td>
<td>58</td>
</tr>
<tr>
<td>4Field</td>
<td>109</td>
<td>108</td>
<td>93</td>
<td>66</td>
</tr>
</tbody>
</table>

* p < 0.05
## Patient-Reported Fecal Incontinence (PRO-CTCAE)

**PRO-CTCAE score 3+ Fecal Incontinence Interference**

<table>
<thead>
<tr>
<th>Time</th>
<th>IMRT</th>
<th>4Field</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 5 of RT</td>
<td>92</td>
<td>109</td>
</tr>
<tr>
<td>4-6 Weeks Post-RT</td>
<td>88</td>
<td>108</td>
</tr>
<tr>
<td>1 Year Post-RT</td>
<td>87</td>
<td>93</td>
</tr>
<tr>
<td>3 Years Post-RT</td>
<td>58</td>
<td>66</td>
</tr>
</tbody>
</table>

**PRO-CTCAE score 3+ Fecal Incontinence Frequency**

<table>
<thead>
<tr>
<th>Time</th>
<th>IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 5 of RT</td>
<td></td>
</tr>
<tr>
<td>4-6 Weeks Post-RT</td>
<td></td>
</tr>
<tr>
<td>1 Year Post-RT</td>
<td></td>
</tr>
<tr>
<td>3 Years Post-RT</td>
<td></td>
</tr>
</tbody>
</table>

* * p < 0.05
**Patient-Reported Urinary Toxicity (EPIC)**

- **Week 3 of RT**: IMRT = 114, 4Field = 134
- **Week 5 of RT**: IMRT = 111, 4Field = 130
- **4-6 Weeks Post-RT**: IMRT = 106, 4Field = 131
- **1 Year Post-RT**: IMRT = 98, 4Field = 114
- **3 Years Post-RT**: IMRT = 68, 4Field = 78

* p < 0.05
Physician-reported toxicity (CTCAE v4)

- No difference between arms

<table>
<thead>
<tr>
<th></th>
<th>Acute Toxicity Grade 2+</th>
<th>Late Toxicity Grade 2+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GI</td>
<td>GU</td>
</tr>
<tr>
<td>IMRT</td>
<td>26.4%</td>
<td>4.6%</td>
</tr>
<tr>
<td>4 Field</td>
<td>21.5%</td>
<td>6.0%</td>
</tr>
<tr>
<td>p value</td>
<td>0.35</td>
<td>0.60</td>
</tr>
</tbody>
</table>
Quality of Life – FACT-G Total Score

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 5 of RT</th>
<th>4-6 weeks post-RT</th>
<th>1 Year</th>
<th>3 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRT Pelvic RT</td>
<td>107</td>
<td>91</td>
<td></td>
<td>89</td>
<td>86</td>
</tr>
<tr>
<td>4 Field Pelvic RT</td>
<td>124</td>
<td>110</td>
<td></td>
<td>111</td>
<td>94</td>
</tr>
</tbody>
</table>
Conclusions

• In comparison with 3DCRT, IMRT reduces patient-reported:
  • Acute GI adverse events (EPIC Bowel and PRO-CTCAE diarrhea and fecal incontinence at 5 wks of RT)
  • Acute urinary adverse events (EPIC Urinary at 5 wks of RT)
  • Late GI adverse events (PRO-CTCAE diarrhea at 1 year post-RT)
  • Late urinary adverse events (EPIC Urinary at 3 years post-RT)

• No difference in disease outcomes at 2 years.
Acknowledgments…

Stephanie Pugh, PhD
NRG Oncology Statistics and Data Management Center

Ann Klopp, MD, PhD
MD Anderson Cancer Center

Karen Gil, PhD
Summa Akron City Hospital/Cooper Cancer Center

Lari Wenzel, PhD
UC Irvine Health/Chao Family Comprehensive Cancer Center

Shannon N. Westin, MD, MPH
MD Anderson Cancer Center

Andre Konski, MD, MBA, MA, FACR
Chester County Hospital

J. Spencer Thompson, MD
University of Oklahoma Health Sciences Center

Desiree E. Doncals, MD
Summa Akron City Hospital/Cooper Cancer Center

Guilherme H.C. Cantuaria, MD
Northside Hospital

This project was supported by grants UG1CA189867 (NCORP) from the National Cancer Institute (NCI)

London Regional Cancer Program

Amy Chang, MD
Pamela Youde Nethersole Eastern Hospital

Vijayananda Kundapur, MD
Saskatoon Cancer Centre

Dasarahally S. Mohan, MD
Kaiser Permanente Cancer Treatment Center

Michael L. Haas, MD
Reading Hospital

Yong Bae Kim, MD
Yonsei University Health System

Catherine L. Ferguson, MD
Georgia Regents University

Lisa A. Kachnic, MD
Vanderbilt University/Ingram Cancer Center

Deborah Bruner, PhD
Emory University/Winship Cancer Institute

David P. D’Souza, MD
Questions
GOG 0273 Secondary Endpoint

William Tew, MD
Associate Attending Clinical Director
Gynecologic Medical Oncology
Memorial Sloan Kettering Cancer Center
GERIATRIC ASSESSMENT AND OUTCOMES WITH CARBOPLATIN AND WEEKLY LOW-DOSE PACLITAXEL IN ELDERLY WOMEN WITH OVARIAN, PRIMARY PERITONEAL OR FALLOPIAN TUBE CANCER: A GYNECOLOGIC ONCOLOGY GROUP STUDY (GOG273, Arm 3).

William Tew, Helen Huang, Vivian Von Gruenigen, Arti Hurria, Thomas Herzog, Lisa Landrum, Ritu Salani, Shashikant Lele, Michael Pearl, Angeles Alvarez Secord, James Fiorica, Tina Rizack, William E. Richards, Gini Fleming

1Dept of Medicine, Gynecologic Medical Oncology Service, Memorial Sloan Kettering Cancer Center, NY, 2GOG Statistics and Data Center, Buffalo, NY, 3Summa Akron City Hospital, Akron, OH, 4City of Hope, Duarte, CA, 5University of Cincinnati Cancer Institute, Cincinnati, OH, 6University of Oklahoma, OK, 7The Ohio State University Wexner Medical Center, OH, 8Roswell Park Cancer Institute, Buffalo, NY, 9Stony Brook University Hospital, Stony Brook, NY, 10Duke Cancer Center, NC, 11Indiana University, Bloomington, 12Women and Infants Hospital Rhode Island, RI, 13Candler Hospital, GA, 14University of Chicago, Chicago, IL, United States
Disclosures

• No conflicts of interest needed to disclose
Ovarian Cancer in Older Adult

- Median Age = 64yo;
  - One-third are 70yo or older.

- Older women with ovarian cancer:
  - 2-fold increased death risk.
    - Higher co-morbidities
    - Less likely to undergo complete staging surgery and receive standard chemotherapy
    - Delay in diagnosis and treatment
    - Higher toxicity to treatments
    - Different biology
### GOG Upfront trials

<table>
<thead>
<tr>
<th>Trial: Platinum-based upfront tx</th>
<th>Age &gt;60</th>
<th>Age &gt;70 (30% US OvCa population)</th>
<th>Age &gt;80</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 273 – Arm1/2**</td>
<td>100%</td>
<td>100%</td>
<td>26%</td>
</tr>
<tr>
<td>GOG 262</td>
<td>55%</td>
<td>21%</td>
<td>4%</td>
</tr>
<tr>
<td>GOG 218</td>
<td>50%</td>
<td>18%</td>
<td>2%</td>
</tr>
<tr>
<td>GOG 172</td>
<td>38%</td>
<td>11%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Development of age-specific trials **
GOG 273
This is a prospective observational study, not a comparison of treatment regimens.

Eligibility
Stage I-IV ovarian, peritoneal, or fallopian tube cancer with confirmed adenocarcinoma at age ≥ 70

Investigator decides primary surgery vs. chemotherapy

Regimen 1
Carboplatin AUC 5*
Paclitaxel 135mg/m²
Plus G-CSF
Every 3 weeks X 4

Interval surgical cytoreduction (if no prior primary surgery) and/or further chemotherapy at the discretion of the physician

Regimen 2
Carboplatin AUC 5*
Every 3 weeks X 4

QOL/Geriatric Assessments
For ALL REGIMENS:
Prior to Cycle 1 and cycle 3, then 3-6 weeks after completion of Cycle 4**

All Subjects receiving regimen 1 or 2 will undergo PK sampling on Day 1 and Day 2 of Cycle 1.

Primary Endpoint-
Will baseline IADL be associated with dose adjustment and delays

152 pts (carbo/taxol q3 week)
60 pts (carbo alone)

Once Regimen 1 and 2 complete accrual, these two treatments arms will be closed

*Patients for whom the physician deems a carboplatin dose of AUC 5 to be unsafe, may be given an AUC of 4.

**For patients unable to complete 4 cycles, perform QOL/geriatric assessments at 12-15 weeks after initiating study treatment.
Baseline IADL was associated with:

- Chemo regimen choice
- Chemo completion regardless of dose delay/adjustments
- Grade 3+ toxicity
- Overall survival (in CP group only).

VonGuenigen, Huang, Beumer, Lankes, Tew, Herzog, Hurria et al, Gyn Oncol, 2016
Compare Weekly dd Paclitaxel versus q3 week Paclitaxel, Combined w/ Carboplatin q3 week (BV optional)

GOG 273
This is a prospective observational study, not a comparison of treatment regimens. All patients entered after 8/12/2013 will receive Regiment 3 treatment.

Eligibility
Stage I-IV ovarian, peritoneal, or fallopian tube cancer with confirmed adenocarcinoma at age ≥ 70

Regimen 1
Carboplatin AUC 5*
Paclitaxel 135mg/m²
Plus G-CSF
Every 3 weeks × 4

Regimen 2
Carboplatin AUC 5*
Every 3 weeks × 4

Regimen 3
Paclitaxel 60mg/m²
Weekly (day is optional)
Plus Carboplatin AUC 5* Every 3 weeks × 4

Interval surgical cytoreduction (if no prior primary surgery) and/or further chemotherapy at the discretion of the physician

QOL/Geriatric Assessments For ALL REGIMENS: Prior to Cycle 1 and cycle 3, then 3-6 weeks after completion of Cycle 4**
All Subjects receiving regimen 1 or 2 will undergo PK sampling on Day 1 and Day 2 of Cycle 1.

Once Regimen 1 and 2 complete accrual, these two treatments arms will be closed. Regimen 3 will open as a single arm study
*Patients for whom the physician deems a carboplatin dose of AUC 5 to be unsafe, may be given an AUC of 4.
**For patients unable to complete 4 cycles, perform QOL/geriatric assessments at 12-15 weeks after initiating study treatment.
GOG 273 Arm III: Study Objectives

Primary Objective:
- Explore the association between a baseline Geriatric Risk Score (GRS) and the patient’s ability to complete 4 cycles of carboplatin q3week and paclitaxel qweek without dose reduction or >7-day treatment delays.
- To estimate the percentage of patients who are able to complete 4 cycles of chemotherapy.

Secondary Objectives:
- Explore reasons for treatment delays and dose reductions
- Explore whether age, baseline scores on geriatric measures (function, nutrition, comorbidity) and QOL are correlated with completed 4 cycles of chemotherapy.
- Describe chemotherapy toxicities.
- Describe QOL and other patient reported outcomes over time.
GA Measures (via Arm 1 and 2)

- Instrumental Activities of Daily Living (IADL) (7 items).

- Activities of Daily Living (ADL) (10 items).

- FACT-O (38 items). The FACT-O score ranges 0-152 with a larger score indicating better QOL.

- FACT/GOG-Ntx4 subscale (4 items). The Ntx score ranges 0-16 with a larger score indicating worse neurotoxicity.

- Social Activities (4 items). The social activities score ranges 0-100 with a larger score indicating less limited in social activities.
Geriatric Risk Score (Arm 3)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;=72</td>
<td>2</td>
</tr>
<tr>
<td>Need for assistance in taking medications from (item from IADL).</td>
<td>1</td>
</tr>
<tr>
<td>Limited in walking one block (item from ADL).</td>
<td>2</td>
</tr>
<tr>
<td>Decreased social activity at least sometimes due to health/emotional problem (item from social activity survey).</td>
<td>1</td>
</tr>
<tr>
<td>Number of falls in the last 6 months ≥ 1.</td>
<td>3</td>
</tr>
<tr>
<td>Fair or worse Hearing.</td>
<td>2</td>
</tr>
<tr>
<td>Hemoglobin &lt;10 g/dl.</td>
<td>3</td>
</tr>
<tr>
<td>Creatinine clearance &lt;34 ml/min.</td>
<td>3</td>
</tr>
<tr>
<td>Standard chemotherapy</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>19</strong></td>
</tr>
</tbody>
</table>

2 items removed from CARG score – cancer type and multi/single chemo regimen
106 patients enrolled

2 No treatments

8 Completed one PRO survey
20 Completed two PRO surveys
120 Completed three PRO surveys

2 No baseline
3 No Follow-ups

104 Evaluable for completion status
102 Evaluable for baseline PROs association
99 Evaluable for changes of PROs
### Patient Characteristics:

**Median age** = 78yo (70-92)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Category</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age categories</td>
<td>70-74</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>75-79</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>80-84</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>≥85</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Race</td>
<td>Non Hispanic Black</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Non Hispanic White</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Performance Status</td>
<td>0</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>55</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Stage</td>
<td>I</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>69</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Neoadjuvent Chemo</td>
<td>No</td>
<td>76</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Reduced (Taxel&lt;60 at d1/d8 or auc&lt;5)</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Standard (proposed in study)</td>
<td>87</td>
<td>84</td>
</tr>
<tr>
<td>Starting Carbo AUC</td>
<td>4</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>89</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
Treatment Completion:

Discontinuation:
- 2 withdrew,
- 2 toxicity
- 1 death, cancer
- 1 other, comorbid

Toxicity (n=28):
- 10 Heme
- 6 Other
- 3 GI Toxicity
- 2 Neuropathy
- 1 – Cardiac, Allergy, Pulm, Musc-Skel
<table>
<thead>
<tr>
<th>AE</th>
<th>N</th>
<th>(%)</th>
<th>AE</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>35</td>
<td>(35%)</td>
<td>Hyponatremia</td>
<td>5</td>
<td>(5%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>18</td>
<td>(17%)</td>
<td>Dehydration</td>
<td>5</td>
<td>(5%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9</td>
<td>(9%)</td>
<td>Hyperglycemia</td>
<td>4</td>
<td>(4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9</td>
<td>(9%)</td>
<td>Hypotension</td>
<td>3</td>
<td>(3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>(8%)</td>
<td>Lung Infection</td>
<td>3</td>
<td>(3%)</td>
</tr>
<tr>
<td>Vomit</td>
<td>7</td>
<td>(7%)</td>
<td>Dyspnea</td>
<td>3</td>
<td>(3%)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>7</td>
<td>(7%)</td>
<td>Sepsis</td>
<td>2</td>
<td>(2%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>(6%)</td>
<td>Ab pain</td>
<td>2</td>
<td>(2%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6</td>
<td>(6%)</td>
<td>Neutropenic Fever</td>
<td>2</td>
<td>(2%)</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>6</td>
<td>(6%)</td>
<td>Hypoalbuminemia</td>
<td>2</td>
<td>(2%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>5</td>
<td>(5%)</td>
<td>Neuropathy</td>
<td>1</td>
<td>(1%)</td>
</tr>
<tr>
<td>Other AEs</td>
<td>1</td>
<td>(1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Baseline GRS:**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Yes</th>
<th>No</th>
<th>unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;=72</td>
<td>89 (86%)</td>
<td>15 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>Need for assistance in taking medications</td>
<td>7 (7%)</td>
<td>94 (90%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Limited in walking one block</td>
<td>56 (54%)</td>
<td>44 (42%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Decreased social activity at least sometimes due to</td>
<td>63 (61%)</td>
<td>37 (36%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>health/emotional problem</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of falls in the last 6 months ≥ 1.</td>
<td>15 (14%)</td>
<td>89 (86%)</td>
<td>0</td>
</tr>
<tr>
<td>Fair or worse Hearing.</td>
<td>18 (17%)</td>
<td>86 (83%)</td>
<td>0</td>
</tr>
<tr>
<td>Hemoglobin &lt;10 g/dl.</td>
<td>9 (9%)</td>
<td>95 (91%)</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine clearance &lt;34 ml/min.</td>
<td>11 (11%)</td>
<td>93 (89%)</td>
<td>0</td>
</tr>
<tr>
<td>Standard chemotherapy</td>
<td>87 (84%)</td>
<td>17 (16%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Completed in 98 patients (all 9 questions answered).*

**Standard chemo defined as carbo (AUC 5) and Weekly paclitaxel (60mg/m2)**
- Mean GRS was 6.5, median was 6 (range 3-15)
- No association with GRS and ability to complete 4 cycles of chemo
- Odds ratio 1.12 (95% 0.093 – 1.34; p=0.23) without dose adjustment
- Odds ratio 1.14 (95%: 0.78 – 1.68; p=0.5) with dose adjustment
Association of GA variables with Grade 3+ Toxicity

<table>
<thead>
<tr>
<th>Geriatric Measures</th>
<th>Odd Ratio</th>
<th>Unit</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic Assessment Score</td>
<td>1.08</td>
<td>1 point</td>
<td></td>
<td>0.393</td>
</tr>
<tr>
<td>Age</td>
<td>0.94</td>
<td>5 years</td>
<td></td>
<td>0.739</td>
</tr>
<tr>
<td>IADL</td>
<td>0.79</td>
<td>1 point</td>
<td></td>
<td>0.019</td>
</tr>
<tr>
<td>ADL</td>
<td>0.92</td>
<td>10 points</td>
<td></td>
<td>0.281</td>
</tr>
<tr>
<td>Social Activities</td>
<td>0.88</td>
<td>10 points</td>
<td></td>
<td>0.168</td>
</tr>
<tr>
<td>FACT-O</td>
<td>0.87</td>
<td>10 points</td>
<td></td>
<td>0.176</td>
</tr>
<tr>
<td>BMI</td>
<td>1.02</td>
<td>1 point</td>
<td></td>
<td>0.644</td>
</tr>
<tr>
<td>Weightloss within 6 Months(%)</td>
<td>0.99</td>
<td>5%</td>
<td></td>
<td>0.954</td>
</tr>
<tr>
<td>Comorbidity(N)</td>
<td>1.22</td>
<td>1 point</td>
<td></td>
<td>0.381</td>
</tr>
</tbody>
</table>

A larger score indicates more independent or better QOL in IADL, ADL, Social Activities, and FACT-O.
<table>
<thead>
<tr>
<th>PRO Measures</th>
<th>Baseline Mean(SD)</th>
<th>Pre-cycle 3 Mean(SD)</th>
<th>3~6 weeks post cycle 4 Mean(SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IADL</td>
<td>11.7(2.4)</td>
<td>12.0(2.1)</td>
<td>11.9(2.4)</td>
<td>0.47</td>
</tr>
<tr>
<td>ADL</td>
<td>42.1(28.2)</td>
<td>49.5(25.9)</td>
<td>48.7(24.4)</td>
<td>0.042</td>
</tr>
<tr>
<td>Social Activities</td>
<td>50.6(23.4)</td>
<td>57.5(21.4)</td>
<td>58.1(20.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>FACT-O</td>
<td>112.8(21.3)</td>
<td>119.5(18.2)</td>
<td>119.1(17.3)</td>
<td>0.004</td>
</tr>
<tr>
<td>FACT/GOG-Ntx subscale</td>
<td>14.2(2.9)</td>
<td>14.0(2.8)</td>
<td>13.2(3.5)</td>
<td>0.011</td>
</tr>
</tbody>
</table>
Conclusions

• Carboplatin (AUC 5) and weekly paclitaxel (60mg/m2) is well tolerated.

• Despite ~65% G3+ tox rate, almost all completed 4 cycles of treatment
  • 66% without dose reduction or more than 7-day delays
  • 29% with dose adjustments

• Geriatric risk score was not associated with dose reduction / delays.

• Limitations:
  • CARG risk score was developed to predict grade 3-5 toxicity.
  • All study patients started at low doses of chemotherapy.
  • Older but fit (85% PS 0-1) patient population.
  • We stopped at 4 cycles – not 6 cycles – to include NACT patients who would undergo interval surgery.

• As in GOG 273 Arm 1 and 2, IADL remains an important and is associated with chemotherapy toxicity.

• Quality of life, ADLs, neuropathy and social activity improved over time.
Questions