NRG Oncology Overview
NRG Oncology Chairmen & Principal Investigators

Walter J. Curran, Jr. MD
Robert Mannel, MD
Norman Wolmark, MD
NRG Oncology Group: “Outstanding” (23)

“Overall impact of the proposed NRG Oncology Group to exert a sustained and powerful influence on the research activities and success is high in the proposed seven disease areas (Brain, Breast, GI, GU, Gynecological, Head & Neck, and Lung Cancers)”
NRG Oncology Mission

To improve cancer patients’ lives by conducting multi-institutional paradigm-defining research emphasizing gender-specific malignancies such as gynecologic, breast, and prostate cancers and localized or locally advanced cancers of all types.
NRG Oncology’s Seven Cancer Disease Site Domains

• Brain Tumors - primary and secondary
• Breast Cancer
• Gastrointestinal Cancers
• Genitourinary Cancers - emphasis on localized and locally advanced prostate cancer
• Gynecologic Cancers: All Subcategories
• Head and Neck Cancer
• Lung Cancer - localized or locally advanced
<table>
<thead>
<tr>
<th>Disease Site</th>
<th>Activations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain Tumor</td>
<td>4</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>5</td>
</tr>
<tr>
<td>GI- colorectal Cancer</td>
<td>1</td>
</tr>
<tr>
<td>GI-non colorectal Cancer</td>
<td>2</td>
</tr>
<tr>
<td>GU Cancer</td>
<td>3</td>
</tr>
<tr>
<td>Gynecologic Cancer</td>
<td>10</td>
</tr>
<tr>
<td>Head &amp; Neck Cancer</td>
<td>3</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>2</td>
</tr>
<tr>
<td>NCORP</td>
<td>4</td>
</tr>
<tr>
<td>Joint studies (COG and SWOG)</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>36 Study Activations</strong></td>
</tr>
</tbody>
</table>
Currently Active NRG Oncology Trials by Disease Site

<table>
<thead>
<tr>
<th>Disease Site</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain Tumor</td>
<td>3</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>7</td>
</tr>
<tr>
<td>GI- colorectal Cancer</td>
<td>1</td>
</tr>
<tr>
<td>GI-non colorectal Cancer</td>
<td>4</td>
</tr>
<tr>
<td>GU Cancer</td>
<td>4</td>
</tr>
<tr>
<td>Gynecologic Cancer</td>
<td>16</td>
</tr>
<tr>
<td>Head &amp; Neck Cancer</td>
<td>3</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>3</td>
</tr>
<tr>
<td>NCORP</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>44</strong></td>
</tr>
</tbody>
</table>

44 Actively Enrolling
NRG Oncology Membership

- 1,925 Participating Sites
- 149 Main Member Sites
- 30 LAPS
- 42 NCORPs + Minority NCORPs
NRG Oncology Accrual Since 3/14

- Total Accrual to NRG Trials: 14,468
- Accrual Credited to Other LPOs: 1,042
- Accrual to Other LPOs Credited to NRG: 4,737
NRG Oncology Publications Since 3/14

Abstracts 359
E-Pub/Published 339

Total 698
NRG Oncology Five Specific Aims 2014-2019

1. Improve adult patients’ lives with localized or locally advanced malignancies;

2. Conduct practice-defining late phase research for the major gender-specific malignancies (breast and gynecologic cancers and prostate cancer) while capitalizing on common biologic features and interactive research opportunities among these diseases;

3. Identify advances in radiation oncology, imaging, surgery, and/or IT for testing in the management of patients with localized and locally advanced malignancies
NRG Oncology Five Specific Aims 2014-2019

4. Integrate and expand the legacy groups’ translational science to better inform the use of biomarker- and biologic pathway-defined approaches to risk stratification, investigational therapy assignment, and clinical trial decision-making;

5. Expand the early phase gynecologic cancer developmental therapeutics program to NRG’s other six cancer disease site committees (Brain Tumor, Breast Cancer, GI Cancer, GU Cancer, Head & Neck Cancer, & Lung Cancer), a strategy which strengthens the selection process of investigational approaches tested in the group’s randomized phase II and III trials.
Specific Aim 1

Improve Patients’ Lives with Localized/Locally Advanced Malignancies

1. Toxicity Reduction or Amelioration (NCORP)
   1. Hippocampal Sparing Whole Brain RT: Therapeutic or PCI
   2. Decreased Intensity Therapy for HPV+ Oropharyngeal Cancer

2. Therapeutic Intensification for Increased Cure/Tumor Control
   1. Adaptive Design for RT Dose Escalation for Lung Cancer
   2. Hypofractionated RT for Many Malignancies

3. Testing of Biomarker-Informed Decision-Making
   1. MGMT/Methylation in Malignant Glioma
   2. Epstein Barr Virus DNA in Nasopharyngeal Cancer
Featured Trial

NRG Oncology/BN002: Phase I Study of Ipilimumab, Nivolumab, and the Combination in Patients with Newly Diagnosed Glioblastoma

- This study is a complex, multiform immune checkpoint inhibitor using single and double ICI combos in GBM.

Featured Publication

Survival and progression-free survival improved when chemotherapy (procarbazine, CCNU, and vincristine) is added to standard RT for low-grade glioma patients. (RTOG 9801) 2016 NEJM:374(14)
Hippocampal Sparing and RT Toxicity Background

- **Neurocognitive toxicity of Cranial RT, including PCI**
  - LA-NSCLC (RTOG 0214): ↑ed decline in HVLT-R + -DR at 3, 6 and 12 mos after PCI vs. observation\(^1\)
  - SCLC (RTOG 0212): Std-dose PCI a/w 62% rate of chronic neurocognitive toxicity, 29% rt of HVLT-DR decline at 6 mos\(^2\)
  - RTOG 0212/0214 2ndary analysis: PCI a/w decline in HVLT and self-reported cognitive functioning\(^3\)

- **RTOG 0933\(^4\): Hippocampal neurogenesis important to memory function and sensitive to cranial RT**

- **In setting of small cell lung cancer, hippocampal relapse risk after HA-PCI estimated to be ~5%\(^5,6\)**

\(^1\)Sun JCO 2011  \(^2\)Wolfson IJROBP 2009  \(^3\)Gondi IJROBP 2013  \(^4\)ASTRO Plenary 2013  \(^5\)Gondi R&O 2010  \(^6\)Kundapur ASCO 2013
Hippocampus Delineation by Software
IMRT can achieve significant RT dose reduction (hippocampus), while delivering 30 Gy to the rest of the brain.
As contouring proceeds postero-cranially, the anterior boundary of the hippocampus is defined by the anterior edge of the temporal horn, to distinguish the hippocampus from the T1-hypointense gray matter of the amygdala, lying anterior and superior to the hippocampus. The medial boundary of the hippocampus is defined by the “boomerang-shaped” uncus.

RTOG 0933: ASTRO 2013 Plenary /JCO 2014

Gondi, et al

- 113 Pts Enrolled in Phase II Conformal Avoidance of Hippocampus During WBRT
- HVLT Score at 4 and 6 Months: No Change
- Historic Control with WBRT: 15% Decline
NRG NCORP CC003: Phase IIR/III Trial Prophylactic Cranial Irradiation with or without Hippocampal Avoidance for Small Cell Lung Cancer

PIs: M Mehta + V Gondi

**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: 304 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. 198 analyzable pts

**Activated December 7, 2015**
NRG NCORP CC001: Phase III Trial Memantine and WBRT with or without Hippocampal Avoidance in Patients with Brain Metastases

PIs: P Brown + V Gondi

Basic Eligibility: Brain Mets 5mm outside hippocampus; KPS≥70; MRI scan

Basic Statistical Design:
Cognitive fxn failure 53.8% at 6 months with WBRT vs. 42.8% with HA-WBRT. 388 analyzable pts.

Sample Size: 510 patients

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

Activated July 2015
NRG Oncology Head and Neck Cancer Committee

Featured Trial

NRG Oncology/HN001: Randomized Phase II and Phase III Studies of Individualized Treatment for Nasopharyngeal Carcinoma Based on Biomarker Epstein Barr Virus (EBV) Deoxyribonucleic Acid (DNA)

- Phase II of this trial (detectable plasma EBV DNA cohort) will determine whether substituting adjuvant CDDP and 5-FU with gemcitabine and paclitaxel will result in superior progression-free survival.

- Phase III (undetectable plasma EBV DNA cohort) will determine whether omitting adjuvant CDDP and 5-FU (observed alone in the adjuvant setting) will result in noninferior overall survival as compared with those patients receive adjuvant CDDP and 5-FU chemotherapy.

Featured Publication

Biomarker Discovery & Validation/Toxicity Reduction:
NRG HN002 - Randomized Phase II Trial for HPV+, Locoregionally Advanced Oropharyngeal Cancer Non-Smoking Pts

Eligibility
- Oropharyngeal SCC
- HPV+
- ≤10 pack-year
- T1-T2 N1-N2b
- T3 N0-N2b

60 Gy radiation (2.0 Gy/fx) in 6 weeks + concurrent cisplatin 40 mg/m² weekly x 6 cycles

60 Gy radiation (2.0 Gy/fx, at 6 fx/week) in 5 weeks

Total sample size: 350
2 years of accrual
2-year follow up

COMPLETED ACCRUAL
REPLACEMENT CONCEPT BEING PROPOSED

1° end point: Select the arm with 2y PFS >91% with lower confidence interval > 85%
QOL (swallowing function) is a strong component of 2nd end point
Therapeutic Intensification
NRG 1106: Stage III Lung Cancer
Adaptive RT Based on Mid-Course PET Response

REGISTRATION

PRE-TX FDG-PET/CT (FMISO-PET/CT) IMAGING

STRATIFIED RANDOMIZATION (TUMOR SIZE, NODAL DISEASE, HISTOLOGY)

ARM 1: CONCURRENT CHEMO-RT
RT to 50 Gy (2 Gy/Fx)
Carboplatin/Paclitaxel Weekly

ARM 2: CONCURRENT CHEMO-RT
RT to 48.3 Gy (2.3 Gy/Fx)
Carboplatin/Paclitaxel Weekly

DURING-TX FDG-PET/CT IMAGING (AFTER FX 18-19 BOTH ARMS)

ARM 1: CONTINUE RT
Same RT plan to 60 Gy total (30 Fx)

ARM 2: ADAPTIVE RT
Based on during-tx FDG-PET RT 2.0 – 3.9 Gy/Fx up to 74 Gy individualized by MLD

CONSOLIDATIVE CHEMOTHERAPY
PET-Adapted Radiation Therapy
NRG/RTOG 1106

Initial PET/CT

Mid-Tx PET/CT

RTOG 1106
~3 wks
NRG HN001 - Phase III EBV(+) Nasopharyngeal Cancer International Trial

**EBV DNA**
- T≥2b or N+
- WHO I-III
- EBV DNA+

**REGISTER**

**EBV DNA**
- IMRT (70 Gy) + CDDP

**EBV DNA**
- EBV DNA neg
- EBV DNA pos

**R1**
- Observe
- N = 632
- CDDP + 5FU x3

**R2**
- Gem
- Paclitaxel x 3
- N = 126

EBV assay harmonization completed Concept & funding approved 7/13, protocol approved 2/14
FD&A IDE approval 3/14, protocol activated 4/14

Enrollment: 232
NRG Working Group for Incorporation of Digital Health Technologies in Oncology Research

Adam Dicker, MD, PhD
Sidney Kimmel Cancer Center
Thomas Jefferson University

Heather Jim, PhD
Moffitt Cancer Center
Passive Activity and Sleep Monitoring

MiniMitter Actiwatches

Actigraph Link

Jim et al. Health Psychol 2013; 32: 768-774
Is It Technically Feasible?

- Pulse/EKG
- Motion
- Orientation
- Glucose
- Blood Pressure
- Oxygen Saturation
- Weight
- Respiration
- Temperature
- Hydration
- Brain Activity
- Skin Conductance

Is It Clinically Relevant?

- Analyzed data is transmitted to providers to monitor

Is It Cost Effective?

ROI = \frac{\text{Outcomes} - \text{Program Cost}}{\text{Program Cost}}

Example: Remotely Monitoring High Risk Oncology Patients is Technically Feasible, Clinically Relevant and Financially Effective

Patients capture weight, temp, BP, pulse, PROs

Remote monitoring reduces hospital and ER admissions
Specific Aim 2
Research in Major Gender-Defined Malignancies

Conduct practice-defining late phase research for the major gender-specific malignancies (breast & gynecologic cancers & prostate cancer) while capitalizing on common biologic features and interactive research opportunities among these diseases.
NRG Oncology Breast Cancer Committee

Featured NRG Breast Cancer Trial
NRG Oncology/NSABP B-51/RTOG 1304: Phase III Trial Evaluating Post-mastectomy RT and Post-lumpectomy Nodal XRT in Patients with Documented Positive Axillary Nodes Before Neoadjuvant Chemo Who Convert to Pathology Negative Axillary Nodes After Neoadjuvant Chemo.

Committee Chairs
Eleftherios P Mamounas, MD
Julia R. White, MD

Committee Co-Chair
Paul A. DiSilvestro, MD

Featured NRG Publication
NRG BR-004 Approved Concept

HER2-Positive, First-line Metastatic Breast Cancer

STRATIFICATION
- Prior adjuvant or neoadjuvant trastuzumab (yes; no)
- Prior adjuvant or neoadjuvant pertuzumab (yes; no)
- Estrogen receptor status (positive; negative)

RANDOMIZATION

Arm 1
Weekly Paclitaxel 2 of 3 weeks
+ Trastuzumab + Pertuzumab‡
every 3 weeks until progression

Arm 2
Weekly Paclitaxel 2 of 3 weeks
+ Trastuzumab + Pertuzumab‡
every 3 weeks until progression
+ Pembrolizumab 200 mg every 3 weeks until progression or for 2 years

Weekly Paclitaxel (WP): 80 mg/m² IV Days 1 and 8 of an every 3 week cycle for at least 6 cycles
‡ Trastuzumab + Pertuzumab: Trastuzumab IV (administer a loading dose of 8 mg/kg; then 6 mg/kg every 3 weeks until progression) + Pertuzumab IV (administer a loading dose of 840 mg IV; then 420 mg IV every 3 weeks until progression).
NRG BR-003
Schema

Node-Positive or High-Risk Node-Negative
Triple Negative Breast Cancer

Randomization

Dose dense ACx4* Weekly Paclitaxel x 12

Dose dense ACx4* Weekly Paclitaxel x 12 + 3-week carboplatin beginning with WP

Carboplatin: AUC 5
*Pegfilgrastim 6 mg SC on day 2

• BRCA mutation status (positive; negative or unknown)
NRG Oncology Gynecologic Cancer Committee

Featured NRG Gynecologic Cancer Trial
NRG Oncology/GY009: A Randomized, Phase II/III Study of Pegylated Liposomal Doxorubicin and Bevacizumab with and without Atezolizumab in Platinum Resistant Ovarian Cancer

• Explores the role of anti-angiogenics and immune check point inhibitors in combination with cytotoxic therapy in recurrent ovarian cancer patients.

Featured NRG Gynecologic Cancer Publications
Bevacizumab for Advanced Cervical Cancer: Final Overall Survival and Adverse Event Analysis of a Randomised, Controlled, Open-label Phase III Trial (Gynecologic Oncology Group 240): 2017 Lancet

Improved Survival with Bevacizumab in Advanced Cervical Cancer: 2014 NEJM 370(8)734-43
Featured NRG Prostate Cancer Trial
NRG Oncology/GU003: A Randomized Phase III Trial of Hypofractionated Post-Prostatectomy Radiation Therapy (HYPORT) Versus Conventional Post-Prostatectomy Radiation Therapy (COPORT)

- This study seeks to demonstrate that HYPORT does not increase patient-reported GI and GU symptoms over COPORT at the 2-year time point.

Featured NRG Prostate Cancer Publication
Survival improved for men with a rising PSA following radical prostatectomy who received salvage RT plus long-term antiandrogen therapy. (NRG/RTOG 9601) 2017 NEJM:376(5):417-428
Specific Aim 3
Testing Rad Onc, Imaging, Surgical, and/or IT Innovations

1. Radiation Oncology
   1. Testing of Stereotactic RT/Proton Therapy
   2. Center for Innovation in Radiation Oncology (CiRO)

2. Imaging
   1. Alignment with ECOG/ACRIN and IROC
   2. NRG Gynecologic Committee/ECOG/ACRIN Partnerships

3. Surgical Innovations
   1. Robotic (TORS), Devices, Nodal Resections/Atlases
NRG Oncology Lung Cancer Committee

Featured Trial

NRG Oncology/RTOG 1308: Phase III Randomized Trial Comparing Overall Survival After Photon Vs Proton Chemo-RT for Inoperable Stage II-IIIB NSCLC

Committee Chair
Jeffrey D. Bradley, MD

Committee Co-Chairs
Jessica Donington, MD
Martin J. Edelman, MD
Ritsuko Komaki, MD

Featured Publications

Randomized Phase II Study of Preoperative Chemotherapy ± Panitumumab Followed by Consolidation Chemotherapy in Potentially Operable Locally Advanced (Stage IIIa, N2+) Non-Small Cell Lung Cancer (NRG Oncology/RTOG 0839). 2017 J. Thorac. Oncol.: 12(9):1413-1420

Randomized Phase II Study Comparing Prophylactic Cranial Irradiation Alone to Prophylactic Cranial Irradiation and Consolidative Extracranial Irradiation for Extensive-Disease Small Cell Lung Cancer (ED SCLC) (NRG Oncology/RTOG 0937). 2017 J. Thorac. Oncol.: 2017.06.015
NRG Oncology Gastrointestinal Cancer Committee

Featured Trials
NRG Oncology/GI001: Randomized Phase III Study of Focal RT for Unresectable, Localized Intrahepatic Cholangiocarcinoma

NRG Oncology/GI002: A Phase II Clinical Trial Platform of Sensitization Utilizing Total Neoadjuvant Therapy (TNT) in Rectal Cancer.

Featured Publication
CDX2 as a prognostic biomarker in stage II and stage III colon cancer. 2016 NEJM:374(3):211-22
NRG’s Center for Innovation in Radiation Oncology (CiRO)

Specific Aims:
1. Promote innovative RT research within the entire NCTN
2. Foster intergroup collaboration and protocol harmonization in terms of inclusion and description of RT techniques and delivery devices

Accomplishments:
• Imaging and RT Questionnaire
• Radiation Therapy Section Templates
• Structure Library
CiRO: Knowledge-Engineering for Optimized RT Planning

More conformal to tumor

Sparing the heart
CiRO’s Deep Machine Learning for Auto-Contour

Correlation plots between hippocampal volumes obtained by our model and the manual segmentation method for 100 test subjects.

Example segmentation result of rectal GTV. **Red**: automatic segmentation  
**Blue**: manual segmentation  
Training: 33 subjects, Testing: 31 subjects  
**Current dice: 0.8 median**

✓ Evaluation results shows that the proposed method can achieve promising segmentation performance for several different segmentation problems, including brain tumor, hippocampus, and rectal tumor GTV.
NRG-RTOG 1308: Phase III Randomized Trial Comparing Overall Survival after Photon vs Proton Chemo-RT for Stage II-IIIB NSCLC

Stratify Stage
1. IIIA
2. IIIB

GTV
1. <= 130 cc
2. >130 cc

Histology
1. Squamous
2. Non-Squamous

RANDOMIZATION

Arm 1
Photon: Highest achievable dose between 60-70 Gy at 2 Gy, once daily plus platinum-based doublet chemotherapy

Arm 2
Protons: Highest achievable dose between 60-70 Gy (RBE) at 2 Gy (RBE) once daily plus platinum-based doublet chemotherapy

Arms 1 and 2: Consolidation Chemotherapy x 2 is allowed

Plan must meet dose and volume constraints of all OARs
(very different from other trials)
IMRT vs Protons Radiation Dose Distribution
Normal Tissue Toxicity
Heart Dose: Protons vs IMRT

Liao, Chang, Komaki, et al.
Pacific: Progression-free Survival: 2017

<table>
<thead>
<tr>
<th>No. of Events/Total No. of Patients</th>
<th>Median PFS (95% CI)</th>
<th>12-Mo PFS (95% CI)</th>
<th>18-Mo PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durvalumab</td>
<td>214/476</td>
<td>16.8 (13.0–18.1)</td>
<td>55.9 (51.0–60.4)</td>
</tr>
<tr>
<td>Placebo</td>
<td>157/237</td>
<td>5.6 (4.6–7.8)</td>
<td>35.3 (29.0–41.7)</td>
</tr>
</tbody>
</table>

Stratified hazard ratio for disease progression or death, 0.52 (95% CI, 0.42–0.65) Two-sided P<0.001

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 months</td>
<td>476</td>
<td>237</td>
</tr>
<tr>
<td>3 months</td>
<td>377</td>
<td>163</td>
</tr>
<tr>
<td>6 months</td>
<td>301</td>
<td>106</td>
</tr>
<tr>
<td>9 months</td>
<td>264</td>
<td>87</td>
</tr>
<tr>
<td>12 months</td>
<td>159</td>
<td>52</td>
</tr>
<tr>
<td>15 months</td>
<td>86</td>
<td>28</td>
</tr>
<tr>
<td>18 months</td>
<td>44</td>
<td>15</td>
</tr>
<tr>
<td>21 months</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>24 months</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>27 months</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Specific Aim 4

Testing of Biomarker- and Biologic Pathway-Defined Approaches

Examples

1. Lumenal Subtype in Prostate Cancer (F Feng, Dicker)
2. KRAS-Variant in Head and Neck Cancer (Weidhaas)
3. Glioma Molecular Profiling and Recursive Partitioning (Chakravati, Bell)
RTOG 9601
Phase III Trial of Salvage RT +/- Anti-Androgen Rx

Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer

While RTOG 96-01 was positive, not all patients benefitted from early initiation of anti-androgen therapy.
Hypothesis

We hypothesized that, similar to other hormone-associated adenocarcinomas, such as breast cancer,

- Prostate cancer can be subtyped based on luminal or basal features
- This subtyping approach can be used to guide treatment selection in prostate cancer
Prostate Cancer Subtyping

1. The PAM50 test measures the expression of 50 classifier genes and 5 control genes used to identify the intrinsic subtypes of breast cancer (luminal A, luminal B, basal, and Her2)

2. The PAM50 classifier was applied to 1,567 prostate cancer specimens from high-risk patients treated with prostatectomy (with long-term clinical follow-up).
Prostate Cancer Subtypes are Similar to Breast Cancer Subtypes

Breast Cohort
N=232
Expression data and PAM50 algorithm obtained from Parker et al.

Prostate Cohort
N=1567
Prostatectomy samples on a CLIA-certified platform
Studies included: MCI, MCII, DVA, TJU, JHMI, CCF

Zhao et al, JAMA Oncology 2017
Luminal B is Independently Associated with Worse Outcomes

<table>
<thead>
<tr>
<th></th>
<th>P-value</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>0.15</td>
<td>0.99 [0.98-1]</td>
</tr>
<tr>
<td>PSA 10-20 vs. &lt;10</td>
<td>0.29</td>
<td>0.89 [0.71-1.11]</td>
</tr>
<tr>
<td>PSA &gt;20 vs. &lt;10</td>
<td>0.16</td>
<td>0.83 [0.64-1.08]</td>
</tr>
<tr>
<td>Gleason 7 vs. &lt;7</td>
<td>1.3E-03</td>
<td>3.49 [1.63-7.47]</td>
</tr>
<tr>
<td>Gleason 8-10 vs. &lt;7</td>
<td>2.4E-08</td>
<td>8.8 [4.1-18.88]</td>
</tr>
<tr>
<td>Margin status</td>
<td>0.74</td>
<td>1.03 [0.85-1.25]</td>
</tr>
<tr>
<td>SVI</td>
<td>3.5E-07</td>
<td>1.72 [1.39-2.11]</td>
</tr>
<tr>
<td>ECE</td>
<td>0.07</td>
<td>1.23 [0.99-1.54]</td>
</tr>
<tr>
<td>LNI</td>
<td>0.01</td>
<td>1.39 [1.09-1.78]</td>
</tr>
<tr>
<td>Basal vs. LumB</td>
<td>2.0E-04</td>
<td>0.66 [0.53-0.82]</td>
</tr>
<tr>
<td>LumA vs. LumB</td>
<td>5.4E-07</td>
<td>0.55 [0.43-0.69]</td>
</tr>
</tbody>
</table>

Zhao et al, JAMA Oncology 2017
Different Biological Pathways are Up- or Down-regulated in Luminal vs Basal Subtypes
Luminal B is Associated with Response to ADT

Cohorts for Matching
N=780

2:1 matching on ADT
Covariates:
Gleason, PSA, RT, LNI, ECE, SVI, SM

Final Matched Cohort
N=315

Predict response to post-operative ADT

Unpublished data, Zhao et al
Unresolved Questions

• Can luminal/basal classification prospectively identify patients most likely to benefit from AAT?
• Can potent short-term anti-androgen therapy (versus long-term use of older, less potent anti-androgens, per RTOG 9601) improve salvage RT outcomes?
Eligibility
PSA recurrent post-RP with
PSA ≥0.1 and ≤1.0 ng/mL
and at least one of the
following risk features:
• Gleason score 4+3 or greater
• Persistent PSA elevation after RP
• Pathologic pT3 disease

Stratification
1. One vs. multiple risk features
2. Molecular subtype
   (Luminal B vs non-Luminal B)

RANDOMIZE

Arm 1
Salvage RT + 6 months of placebo

Arm 2
Salvage RT + 6 months of apalutamide

The Next Step: Molecular Stratification
NRG 1614 Trial Schema

Trial PIs: F Feng & D Spratt
NRG 1614 Objectives

Primary objective:
To determine whether, in men with post-prostatectomy PSA recurrences, salvage RT with enhanced anti-androgen therapy with apalutamide (ARN-509) will improve time to progression (TTP) compared to RT alone.

Secondary objective:
To determine whether molecular stratification by the PAM50 gene expression clustering will identify subsets of prostate cancer which derive the greatest benefit from anti-androgen therapy.
Innovative Aspects of this Study

- First biomarker-stratified trial related to prostate cancer radiotherapy
- Uses a predictive assay performed in a CLIA-certified lab
- First network group trial to investigate adding next-generation anti-androgen therapy to salvage RT

Clinical data from one NRG trial (RTOG 9601) provided the motivation for developing a biomarker (PAM50) that now is being tested in another NRG trial (1614)
Discovery/Validation Platform for these Biomarker Studies: A High Density Gene Expression Array

- 5.5 million probes on array
- 1.4 million RNA transcripts
- Includes all known protein-coding genes
- Assay performed in a CLIA-certified laboratory in collaboration with GenomeDx Biosciences
## Active NRG Protocols with Biomarker Testing

<table>
<thead>
<tr>
<th></th>
<th>GYN</th>
<th>Breast, Colorectal GI</th>
<th>Brain, H&amp;N, Lung, Non-colorectal GI, GU</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>As of June 30, 2017</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Integral</td>
<td>2</td>
<td>1</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Integrated</td>
<td>5</td>
<td>14</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td>Exploratory</td>
<td>48</td>
<td>13</td>
<td>21</td>
<td>82</td>
</tr>
</tbody>
</table>

*Note: Protocols can have more than one biomarker type*
NRG Oncology CCSC Proposals

<table>
<thead>
<tr>
<th>Disease Site</th>
<th>Feasibility Queries Received</th>
<th>Feasibility Queries Approved</th>
<th>CCSC Proposals Submitted</th>
<th>CCSC Proposals Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 1 through June 30, 2017</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Breast</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cervix</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Corpus</td>
<td>7</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>GI</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GU</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lung</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ovary</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
## NRG Grants Funding Translational Science

<table>
<thead>
<tr>
<th>TS Study</th>
<th>Main Study</th>
<th>Funding Source</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative Supplement</td>
<td>NSABP B-52</td>
<td>U10</td>
<td>Pogue-Geille</td>
</tr>
<tr>
<td>DOD Grant</td>
<td>GOG 0172, 0182, 0218</td>
<td>DOD</td>
<td>Birrer</td>
</tr>
<tr>
<td>GOG 0225</td>
<td>GOG 0225</td>
<td>R01</td>
<td>Thomson</td>
</tr>
<tr>
<td>GOG 0286B</td>
<td>GOG 0286B</td>
<td>U10</td>
<td>Bae-Jump</td>
</tr>
<tr>
<td>GOG 0177</td>
<td>GOG 0177</td>
<td>K12</td>
<td>Grushko</td>
</tr>
<tr>
<td>GOG 8035</td>
<td>GOG 0191, 0219</td>
<td>R21</td>
<td>Tewari</td>
</tr>
<tr>
<td>GOG 0218</td>
<td>GOG 0218</td>
<td>R01</td>
<td>Birrer</td>
</tr>
<tr>
<td>NCTN CSC00009</td>
<td>NSABP C-08</td>
<td>CTEP-CCDP</td>
<td>Zenklusen</td>
</tr>
<tr>
<td>NRG BN TS003</td>
<td>RTOG 0825</td>
<td>R01</td>
<td>Armstrong</td>
</tr>
<tr>
<td>NRG BN TS006</td>
<td>RTOG 0424</td>
<td>R01</td>
<td>Chakravarti</td>
</tr>
<tr>
<td>NRG HN TS002</td>
<td>RTOG 0234</td>
<td>R01</td>
<td>Myers</td>
</tr>
<tr>
<td>RTOG TRP 181</td>
<td>RTOG 0522</td>
<td>R01</td>
<td>Ferris</td>
</tr>
<tr>
<td>RTOG TRP 183</td>
<td>RTOG 9514</td>
<td>R01</td>
<td>Kirsh</td>
</tr>
<tr>
<td>RTOG TRP 204</td>
<td>RTOG 0522</td>
<td>SPORE</td>
<td>Chung</td>
</tr>
</tbody>
</table>

*Submitted for NCTN CTAC Request January 2017*
Specific Aim 5
Expand NRG Oncology Early Phase Research

Expand the early phase gynecologic cancer developmental therapeutics program to NRG’s other six cancer disease site committees (Brain Tumor, Breast Cancer, GI Cancer, GU Cancer, Head & Neck Cancer, & Lung Cancer), a strategy which strengthens the selection process of investigational approaches tested in the group’s randomized phase II and III trials.
Proposed New NRG Specific Aims for 2019-2025

• Current Aims 1-5 Still in Play
• Each Aim Will be Enabled by Two Additional Strategies
  – Testing of Immune Modulation to Fulfill these Aims
  – Applying Precision Oncology Approaches When Appropriate
• Third Strategy: Mobilize Opportunities for Further Collaboration within NCTN and Beyond to Achieve these Aims
Other NRG Oncology Strengths

- Geographically/Academically Distributed Functions for Statistics & Data Management and Biorespository,
- Foundation Trials (>12 Currently Active) Provide Strong Synergy with CTEP and DCP-Aligned Research
- Young Investigator and Pilot Grant Funding in Place
- Rigorous Publication Guidelines Established
- Growing International Membership Participation
- Existing Collaborations with Each of Four Other NCTN Groups
NRG Oncology Summary

- Strong Progress in Fulfilling its Specific Aims
- Important Examples of Practice-Defining Results
- Alignment with Science Strong in Many Activities
- Legacy Groups’ Strengths Remain Strong in NRG
- NRG’s Unique Role in NCTN Well Established
- High Value Given to Broader NCTN Participation
Thank You!!!!!!!!!!!!!!!!!!!!!

Speaking on NCTN to National Cancer Advisory Board 2014