National Clinical Trials Network Groups
Update Fall 2014

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NCTN Groups Update

• Why Continue the Groups?
• NCTN Groups vs Cooperative Groups: Any Real Difference?
• NCTN Current Trials: A Few Examples
• NCTN Structure and Governance Challenges
Why Continue the Groups?

• Practice-Defining, Paradigm-Shifting Research
• Cost Effective ($150-160 M/yr NCI Funding for 12 yrs)
  – 90+% Volunteer Physician Effort
  – Cost Effectiveness Confirmed in NCI-Supported Review
  – A System Impossible to Replicate at Current Cost
• Alignment with all major US & Canadian Cancer Centers
• Many Group Trials not Feasible at Centers or with Pharma
Why Change the Groups?

• Institute of Medicine Recommendations 2010
  – More Efficient System with Shorter Timelines
  – Align Groups with New Science More Effectively
  – Restore Groups’ Funding to Recommended Levels
  – Reduce Oversight of NCI over Group Research
  – More Trials for Pts with Rare Malignancies
Is NCTN Meaningfully Different than Old System?

- Fewer Groups: Coordination of Groups Easier
  Reduced Career Opportunities
- Better Coordination: Too Early to Tell
  Need Governance Structure
- More Cost Effective? Unclear
  $ Distribution is Different
- More Timely/ Efficient: Efficiency Efforts in Place
- Rare Disease Trials: No
- Alignment with Science: Already Happening
Current NCTN Lung Cancer Trial Examples

• Precision Medicine Effort in Cancer Trials
  – Lung MAP:       SWOG 1400
  – ALCHEMIST:      Alliance/ECOG ACRIN
  – Stage III Lung Cancer  NRG 1306/Alliance 31101

• Innovative Rad Oncology Trials for Stage III NSCLC Pts
  – Adaptive Radiotherapy  NRG/RTOG 1106
  – Proton Beam vs IMRT   NRG/RTOG 1308

None of These Trials are Doable in Any Other System
LUNG-MAP (S1400): A Biomarker-driven Multi-Arm Master Phase II/III Trial in Squamous Lung Cancer 2nd line Therapy
S1400: LUNG-MAP: Squamous Lung Cancer - 2nd Line Therapy

Biomarker Profiling (NGS/CLIA)

Biomarker A

TT A → CT* → Endpoint PFS/OS

Biomarker B

TT B → CT* → Endpoint PFS/OS

Biomarker C

TT C+CT → CT* → Endpoint PFS/OS

Biomarker D

TT D+E → E* → Endpoint PFS/OS

Biomarker Non-Match

CT*

Non-Match Drug
TT=Targeted therapy, CT=chemotherapy (docetaxel or gemcitabine), E=erlotinib
◊ Archival FFPE tumor, fresh CNB if needed
ALCHEMIST
(Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials)

3 Integrated Trials Testing Targeted Therapy in Early Stage Lung Cancer
ALCHEMIST Rationale

- ALCHEMIST is studying whether or not treatment based on genotype improves cure rates in earlier stage (IB-IIIA) NSCLC cancer patients with non-squamous tumors that have been completely surgically resected.
Resected NSCLC tissue tested on ALCHEMIST Screening Trial

Patients with tumors with an ALK re-arrangement

RANDOMIZE

1 cycle = 21 days

Crizotinib 250 mg po BID x 2 years → Long Term Follow-up

Placebo po BID x 2 years → Long Term Follow-up

Primary endpoint is overall survival
Primary endpoint is overall survival
NRG/RTOG 1306/Alliance 31101

A RANDOMIZED PHASE II STUDY OF INDIVIDUALIZED COMBINED MODALITY THERAPY FOR STAGE III NON-SMALL CELL LUNG CANCER (NSCLC)
NRG/RTOG 1306/ Alliance 31101

Stage III NSCLC With either EGFR TK mutation or ALK Fusion

A Randomized Phase II Trial

- **Experimental**
  - EGFR Mutation +
    - Erlotinib 3 months followed by Chemo-RT*
  - Alk Fusion +
    - Crizotinib 3 months followed by Chemo-RT*

- **Control**
  - EGFR Mutation+/Alk Fusion+
    - Chemo-RT* ONLY

*Pemetrexed 500 mg/m² q 3 weekly x 4 Carboplatin AUC 5 (4 cycles) with Thoracic Radiation 60 Gy
MATCH TRIAL DESIGN

1. Genetic sequencing
   Actionable mutation detected
   Study agent
   Stable Disease, Complete or partial response (CR+PR)
   Continue on study agent until progression
   Progressive disease (PD)
   Check for additional actionable mutations
   Yes
   No additional actionable mutations, or withdraw consent
   Off study
   No

PD
NRG/RTOG 0617: Survival by RT Dose

<table>
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<tr>
<th>Months since Randomization</th>
<th>Patients at Risk</th>
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<tr>
<td></td>
<td>Standard (60 Gy)</td>
</tr>
<tr>
<td>0</td>
<td>213</td>
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<tr>
<td>3</td>
<td>207</td>
</tr>
<tr>
<td>6</td>
<td>190</td>
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<td>15</td>
<td>141</td>
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<tr>
<td>18</td>
<td>108</td>
</tr>
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</table>

Survival Rate (%)

- Standard: 66.9%
- High dose: 53.9%

Median Survival Time
- Standard: 28.7 months
- High dose: 19.5 months

HR = 1.56 (1.19, 2.06)  p = 0.0007
PET-Adapted Radiation Therapy

NRG/RTOG 1106
~3 wks
(47.5 Gy/19 fx @ 2.5 Gy/fx)
NRG/RTOG 1106 tests the efficacy of during-RT PET-MTV based individualized radiation dose escalation.

NRG/RTOG 1106-Adaptive RT for Stage III NSCLC Pts

**NRG/RTOG 1106**
- **1:** Conc. chem- RT 50 Gy/25fx (ED2^\text{\textsuperscript{\textdegree}}=50 Gy)
- **2:** Concurrent chem-RT to ED2^\text{\textsuperscript{\textdegree}}=50 Gy in 17-21 fx.

**RTOG 0617**
- **Uniform RT dose prescription**

**Inoperable or unresectable Stage III NSCLC (FDG-PET/CT staged)**

**Randomize**

**FDG PET/CT at 40-50 Gy ED2^\text{\textsuperscript{\textdegree}} for all pts**

**FDG- PET/CT based RT plan to 74 Gy ED2**

**F-Miso-PET for Selected Institutions**

**Experimental arm:**
- Individualized adaptive RT

**1:** Continue conc. chem-RT to a total of 60 Gy ED2 /37 fx or MLD of 20 Gy

**2:** During-RT FDG-PET/CT adaptive chem-RT to MLD 20 Gy $ in 2.4-3.5$ Gy/fx for 9-13 fx to a total of 86 Gy (100 Gy ED2 lung ) /30 fx
PET-Adapted Radiation Therapy

Initial PET/CT

Mid-Tx PET/CT

NRG/RTOG 1106
~3 wks
Proton Beamline
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)
Heart Dose: Protons vs IMRT

Heart V5

IMRT vs. PSPT - Latest Results

Moving Average of Mean Heart Dose

NRG ONCOLOGY™
3D vs Proton for NSCLC

Photon 3D-CRT

Proton
Are Such Trial Strategies Possible for Other Tumor Types?

• Is there a Biologic +/- or Biophysical Rationale?
• Are there Appropriate Targets +/- or Targeting Agents?
• Does NCTN Have the Resources for Such Strategies?
• Candidate Disease Sites:
  – Melanoma
  – Malignant Brain Tumors
  – Selected Gastrointestinal Cancers
Improved Early Event-Free Survival With Imatinib in Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia: A Children’s Oncology Group Study

Kirk R. Schultz, W. Paul Bowman, Alexander Aledo, William B. Slayton, Harland Sather, Meenakshi Devidas, Chenguang Wang, Stella M. Davies, Paul S. Gaynor, Michael Trigg, Robert Rutledge, Laura Burden, Dean Jostad, Andrew Carroll, Nyla A. Heerema, Naomi Winick, Michael J. Borowitz, Stephen P. Hunger, William L. Carroll, and Bruce Camitta

See accompanying editorial on page 5121 and articles on pages 5168 and 5189

ABSTRACT

Purpose
Imatinib mesylate is a targeted agent that may be used against Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL), one of the highest risk pediatric ALL groups.

Patients and Methods
We evaluated whether imatinib (340 mg/m²/d) with an intensive chemotherapy regimen improved outcome in children ages 1 to 21 years with Ph+ ALL (N = 92) and compared toxicities to Ph- ALL patients (N = 65) given the same chemotherapy without imatinib. Exposure to imatinib was increased progressively in five patient cohorts that received imatinib from 42 (cohort 1; n = 7) to 280 continuous days (cohort 5; n = 50) before maintenance therapy. Patients with human leukocyte antigen (HLA) identical sibling donors underwent blood and marrow transplantation (BMT) with imatinib given for 6 months following BMT.

Results
Continuous imatinib exposure improved outcome in cohort 5 patients with a 3-year event-free survival (EFS) of 80% ± 11% (95% CI, 64% to 90%), more than twice historical controls (35% ± 4%; P < .0001). Three-year EFS was similar for patients in cohort 5 treated with chemotherapy plus imatinib (88% ± 11%; 95% CI, 66% to 96%) or sibling donor BMT (57% ± 22%; 95% CI, 30.4% to 76.1%). There were no significant toxicities associated with adding imatinib to intensive chemotherapy. The higher imatinib dosing in cohort 5 appears to improve survival by having an impact on the outcome of children with a higher burden of minimal residual disease af-
COG: Long-Term Results: Ph+ ALL

7 Year DFS
Chemo + Imatinib 72%
Historical control 27%

Schultz, JCO, 2009; updated Sept 2013
State of Georgia: NCTN Lost Opportunity?

- Historic Underperformer in Cooperative Group Trials
- 2014
  - New LAPS U10 (Winship Cancer Institute)
  - New Minority NCORP (GA Regents/Morehouse)
  - New Georgia CORE NCORP (Many Sites)
  - Savannah Site Participating in Another NCORP
  - 33+% Minority Enrollment at Most Georgia Sites
  - 8th Most Populous State
State of Georgia: Lost NCTN Opportunity?

- Tremendously Expanded Public Cancer Trials Network
- Insufficient Number of NCTN Trials
- Insufficient Number of Patient Slots in NCTN Trials
- All Noted Networks will Reach/Exceed Target Enrollment
- Significant Lost Opportunity?
NCTN Groups Summary

- Amazing Adaptation of Groups to New System!
- Trials in NCTN Limited by Available Resources
- Governance of NCTN Needs Definition
- What are Unintended Consequences of Transition?
- Great Need for Resources in Project Development