Update
Head and Neck Steering Committee

NCI Clinical Trials Advisory Committee
December 8, 2008

Co-Chairs
Arlene Forastiere, M.D.
David Schuller, M.D.
Andrew Trotti, M.D.
Primary Goal

Increase productivity of clinical research involving head and neck cancer patients

“Productivity” defined as --

– answering important clinical and translational questions
– decreasing time to complete trials
– developing biologic correlates
– addressing quality of life issues
Presentation Summary

I. Current Clinical Research Challenges – Schuller

II. HNSC Progress Report – Trotti

III. Suggested HNSC Initiatives to Overcome Challenges– Forastiere
Clinical Research Challenges

• Infrequent malignancy
  – Estimated new cancer cases in US in 2007\(^1\)
    • Prostate \(218,890\)
    • Lung \(213,380\)
    • Breast \(180,510\)
    • Colon \(112,340\)
    • Head and Neck (inc. Thyroid) \(79,210\)

\(^1\)Source: American Cancer Society, Cancer Facts & Figures 2007
Clinical Research Challenges

• Prevalence of older people with substantial co-morbidities
  – contracted treatment tolerance
• Multiple psychosocial needs of study population
  BUT . . .
  • burden of HPV-associated cancers is increasing in the U.S. and Europe
    – predominantly among men
    – younger ages
• HPV ⊕ HN cancer population is seemingly less challenging but with several unknowns still to be defined
Clinical Research Challenges

• Multiple primary malignancies 10-30%
  – prevention strategies integrated into therapeutic trials to improve survival?
• Premalignancies are interventional opportunities
  – cooperation necessary with cancer prevention groups
Clinical Research Challenges

- Contracted cooperative group involvement

**Past**
- SWOG
- ACOSOG
- RTOG
- ECOG

**Current**
- RTOG, ECOG*

*CALGB, SWOG, NCCTG, NCI-C have expertise and eligible patient populations for potential inclusion.
Head and Neck Steering Committee

Progress Report
2008
Overview

• One year in full operation
• Mission: Phase III, Large Phase II
• 4 task forces
• 2 Working Groups
• Reviewed 2 concepts; 1 approved
  RTOG 0811: intermediate risk post-op (RT +/- erbitux) approved
  ACRIN 6685: PET Staging in the N0 Neck in process
• H&N Clinical Trials Planning Meeting:
  HPV-related H&N Cancer, Wash DC, Nov 2008
Head and Neck Task Forces

NCI H&N Steering Committee

- Previously-untreated/locally advanced
- Metastatic & Recurrent Disease
- Tumor Biology & Imaging
- Rare Tumors

Working Groups
H&N Steering Committee Membership

Arlene Forastiere, MD, Co-Chair
David Schuller, MD, Co-Chair
Andy Trotti, MD, Co-Chair

Kian Ang, M.D., PhD
Barbara Burtness, MD
Claudio Dansky Ullmann, MD
Terry Day, MD
Adel El-Naggar, MD, PhD
Boris Freidlin, PhD
Shankar Giri, MD
Jennifer Grandis, MD
Merrill Kies, MD
Marnie Kaufman
Wayne Koch, MD
Marshall Levine, MD

Val Lowe, MD
Mitchell Machtay, MD
Judith Manola, MS
Benjamin Movsas, MD
Brian O'Sullivan, MB
Thomas F. Pajak, PhD
Gamini Soori, MD, MBA
Susan Urba, MD
Carter Van Waes, MD, PhD
Bhadrasain Vikram, MD
Everett Vokes, MD
Greg Wolf, MD
Institutional Membership

- M.D. Anderson Cancer Center
- Fox Chase Cancer Center
- Medical University of South Carolina
- Veterans Affairs Medical Center
- University of Pittsburgh School of Medicine
- Adenoid Cystic Carcinoma Research Foundation
- Greater Baltimore Medical Center
- Mayo Clinic
- Kimmel Cancer Center at Jefferson Medical College
- Thomas Jefferson University
- Dana Farber Cancer Institute
- University of Michigan
- University of Chicago
- National Cancer Institute
- National Institute on Deafness and Other Communication Disorders
- Radiation Therapy Oncology Group
- University of Toronto, Princess Margaret Hospital
- Henry Ford Health System
- Johns Hopkins University
- James Cancer Hospital and Solove Research Institute (Ohio State)
- H. Lee Moffitt Cancer Center
RTOG 0811: A Phase III Study of Postoperative Radiation Therapy (IMRT) +/- Cetuximab for Locally-Advanced Resected Head and Neck Cancer

First reviewed: February 2008
Concept approved: August 2008

ACRIN 6685: FDG PET/CT Staging of Head and Neck Cancer and its Impact on the N0 Neck

Concept reviewed November 2008-outcome pending
Working Groups

1) Endpoints Working Group:

Product #1: Draft document to Steering Committee (January 2009)

2) Expanding Access to Clinical Trials

Product #1: Policy to permit phase II trials to be listed on CTSU endorsed by only one group (done)

Product #2: White Paper on challenges and opportunities (Pending)
Clinical Trials Planning Meeting (CTPM)  
(Formerly State of the Science Meeting)

Squamous Cell Head and Neck Cancer  
and the Human Papillomavirus  
November 9-10, 2008; Wash DC,

70+ participants: Clinicians, Translational Scientists, Epidemiologists  
5 Sessions/Panels  
3 Working Groups (Archived Tissue; Prevention; Trial Design)

Principles of Trial Design for HPV pos trials identified

Proceedings to be published in Journal (Head and Neck)
# Two distinct head and neck cancers

<table>
<thead>
<tr>
<th>Anatomic site</th>
<th>HPV-positive</th>
<th>HPV-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonsil / BOT</td>
<td>Basaloid</td>
<td>Keratinized</td>
</tr>
<tr>
<td>All sites</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histology</th>
<th>Basaloid</th>
<th>Keratinized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td>Gender</td>
<td>3:1 men</td>
<td>3:1 men</td>
</tr>
<tr>
<td>SE status</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Sexual behavior</td>
<td>Alcohol / tobacco</td>
</tr>
<tr>
<td>Incidence</td>
<td>Increasing</td>
<td>Decreasing</td>
</tr>
<tr>
<td>Survival</td>
<td>Improved</td>
<td>Worse</td>
</tr>
</tbody>
</table>

Adapted from M. Gillison
Tumor HPV status and survival

**Figure 3a Overall Survival By HPV**

- **Two-year overall survival**
- Log-rank test, *p*=0.005

- Negative: 95%
- Positive: 62%

Fahkri 2008 JCO
Proportion of all HNSCC that are oropharynx, U.S. 1973-2005

Chaturvedi 2008 JCO
Incidence trends

- Incidence increasing for HPV-related
- Incidence decreasing for HPV-unrelated
- Equalization in 2004

Chaturvedi 2008 JCO
CTPM Consensus

**Principles of HPV Trial Development**

- HPV+ is sufficiently different disease that it requires separate trials (c.f. HPV neg)
- Treatment de-escalation studies focus needed
- Insufficient number, low number of events, of HPV+ patients for a phase III trial
- Feasible: Phase IIR de-escalation trial with toxicity as the primary endpoint
- Stratify for smoking
- Need central reference lab with quick turn around (BISQFP funding; “Integral”)
- All patients should be treated with IMRT technology as SOC
“Conceptual Design”
Reduced Intensity HPV Trial
RIT-HPV Locally Advanced

Primary Endpoint:
Feeding tube rates at 1 year

Secondary Endpoints:
Relative Toxicity Risk
Performance Status Scale-HN
Patient Reported QOL (FACT-HN)
Health Utility Measure (EQ-5D)
Worst-grade method rates of high grade events
Worst-grade method late effects

All patients treated with IMRT technology.
Concepts reviewed by HNSC in 2008

**RTOG 0811**

<table>
<thead>
<tr>
<th>Register</th>
<th>Stratify</th>
<th>Randomize</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2-3, N0-2 or T1, N1-2/M0</td>
<td>EGFR expression</td>
<td><strong>Arm 1: Radiation Therapy Alone</strong></td>
</tr>
<tr>
<td>Oral cavity, oropharynx or larynx</td>
<td>HPV Status</td>
<td>RT, 2 Gy/day, in 30 fractions for a total of 60 Gy</td>
</tr>
<tr>
<td>SCCA</td>
<td>Use of IGRT</td>
<td><strong>Arm 2: Radiation Therapy + Cetuximab</strong></td>
</tr>
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**Mandatory central Analysis of tumor tissue for EGFR and HPV**

**Use of IGRT**

**Arm 1: Radiation Therapy Alone**

RT, 2 Gy/day, in 30 fractions for a total of 60 Gy

**Arm 2: Radiation Therapy + Cetuximab**

At least 5 days prior to RT:

- Cetuximab: Initial dose, 400 mg/m²
- RT, 2 Gy/day in 30 fractions for a total of 60 Gy
- plus Cetuximab: 250 mg/m²/week x 6-7 weeks
  - plus
- Cetuximab: 250 mg/m²/week x 4 weeks post-RT
  - for a total of 11-12 doses
Primary objective: Efficacy, defined as overall survival

Secondary objectives: (summarized)

Acute/Late Toxicity

Progression-free survival (PFS) and time to local-regional progression

Tumor analysis of EGFR, HPV infection, DNA for KRAS and TP53 mutations, RNA analyses of gene expression profiles, and germline DNA analyses of polymorphic variants in EGFR intron repeats for associations w/outcome

Patient-reported quality of life

Tertiary objective (Exploratory): To evaluate the utility of IGRT as a means of enhancing the efficacy of local-regional control of IMRT while reducing the acute and/or late toxicity and improving patient-reported outcomes
Primary objective:

Determine the negative predictive value (NPV) of PET/CT for the N0 neck

Secondary objective:

Estimate the sensitivity of PET/CT for occult metastasis in the clinically N0 neck

Analyze cost-effectiveness of using PET for staging of head and neck cancer;

Estimate the impact of occult distant body metastasis discovered by whole body PET/CT;

Correlate PET/CT findings to biomarker results;

Evaluate quality of life, particularly in participants
ACRIN 6685 cont’d

Inclusion Criteria:

1. Newly diagnosed SCC head and neck cancer;

2. Bilateral neck dissection planned for care (both necks required).

3. At least one neck is clinically N0 as defined by physical exam and CT or MRI

4. Stages T2, T3, or T4. N0–N3, excluding N2c for bilateral disease

5. Patients in whom it may be considered a viable clinical option to perform bilateral neck dissection when primary cancers are at high risk for bilateral metastasis. These will include: 1) oral cavity cancer, 2) oropharynx cancer, 3) larynx, 4) supraglottic cancer.
Goal to Increase Productivity of Clinical Research in H & N Cancer

• Squamous cell cancers of all stages
  – Tobacco/alcohol-associated
  – Virus-associated (HPV**)

• Rare diseases (unmet need)
  – Salivary gland cancer
  – Sinus
  – Thyroid cancer
Opportunity to Accelerate
Bench  ↔  Bedside Discovery

- SC is inclusive: brings the major thought leaders in HN oncology to the table
- Structure of disease and tumor stage TFs and a biology and imaging TF to promote standards and QA
- Access to established tissue banks and ability to carry out prospective serial tissue sampling
Opportunity to Accelerate
Bench $\iff$ Bedside Discovery

• Exploit existing CTEP relationship with industry for evaluation of combination regimens
• Exploit the relationship of academic head and neck cancer research programs with industry
  – Industry pipeline of targeted therapeutics
  – Industry’s interest in H & N cancer (coming to us)
  – Infrastructure and funding support
  – Access to patients
Opportunity to Accelerate
Bench ↔ Bedside Discovery

• Foundations and Advocacy Groups
  – Fundraising for research focused on their cause
  – Information provided to their constituencies
  – Push for more clinical trial options
  – Ultimate goal of more therapeutic options and curative therapies
Head and Neck Task Forces

NCI H&N Steering Committee

- ECOG, RTOG
- Previously-untreated/
  Locally advanced
- Metastatic &
  Recurrent Disease
- Rare Tumors

Working Groups

- Tumor Biology
  & Imaging
- Clinical Trial
  Networks
- Foundations & Advocacy Groups

Foundations & Advocacy Groups

- CALGB
- SWOG
- NCIC
- NIDCR
- SPORES
Leveraging of the Steering Committee Structure to Enhance Clinical Research

• **Prioritization** of clinical research questions
  – Mandate to TFs (first result – HPV CTPM)

• **Communication** among stakeholders
  – Eliminate redundancy
  – Develop the best scientific trial designs

• **Expansion** of partnerships to
  – Increase trial participation among physicians
  – Increase patient accrual and speed trial completion
  – Engage industry and advocacy groups
Head and Neck Cancer
Leveraging Opportunities

• HPV-oropharynx cancer CTPM (Nov 9-10, 2008)
  – Highly successful
  – Next step to develop and submit concept for SC review
  – Opportunity to invest multiple stakeholders in the process and outcome of this trial
Head and Neck Cancer Leveraging Opportunities

• Salivary gland cancer workshop (NIDCR & ACCRF Nov 17-18, 2008)
  – Specimen biorepository established
  – Formation of a consortium of academic centers: Cleveland Clinic, Univ. Chicago, Univ. Wisconsin, Univ. Michigan, Univ of Washington, MDA, MSKCC, Johns Hopkins, DFCI, Princess Margaret Hospital; Rare tumors TF chair and NIDCR investigators
  – Next step to initiate concept development for SC review
Protocol Development and Implementation

- ECOG, RTOG
  - CALGB
  - SWOG
  - NCIC
  - NIDCR
  - SPORES
  - Clinical Trial Networks
  - Foundations & Advocacy Groups

Collaborative Concept and Protocol Development

- RTOG or ECOG statistical & operations office
- Study Co-Chairs to include major contributors outside of the lead coop group

Activation through CTSU

Per case payment to offset institutional costs for non-ECOG/RTOG member
Protocol and Concept Development

Authorship: Define new criteria that incorporate scientific contribution and accrual to be agreed upon by all cooperative groups
Summary

• Opportunity
  – To address the most critical questions
  – To engage all the stakeholders
  – To substantially increase accrual and trial completion time
Summary

• Obstacles
  – Contracted number of cooperative groups with head and neck committees
  – No mechanism for investigators outside of RTOG and ECOG to submit protocols for CTEP/NCI activation
  – No mechanism for investigators outside of RTOG and ECOG to get academic/trial leadership credit
  – Academic leaders turn to industry which then becomes a competitor, instead of a partner, siphoning ideas and patients
Summary

• Proposed solution
  – Collaborative process of concept and protocol development
  – Co-Chair status of non-ECOG/RTOG member on trial “sponsored” by ECOG or RTOG
  – Per case payment to offset institutional costs of trial participation
  – New cooperative group authorship guidelines
  – Partner with industry and with foundations and advocacy groups