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		Current
SWOG		
ACOSOG	⟶	RTOG, ECOG*
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

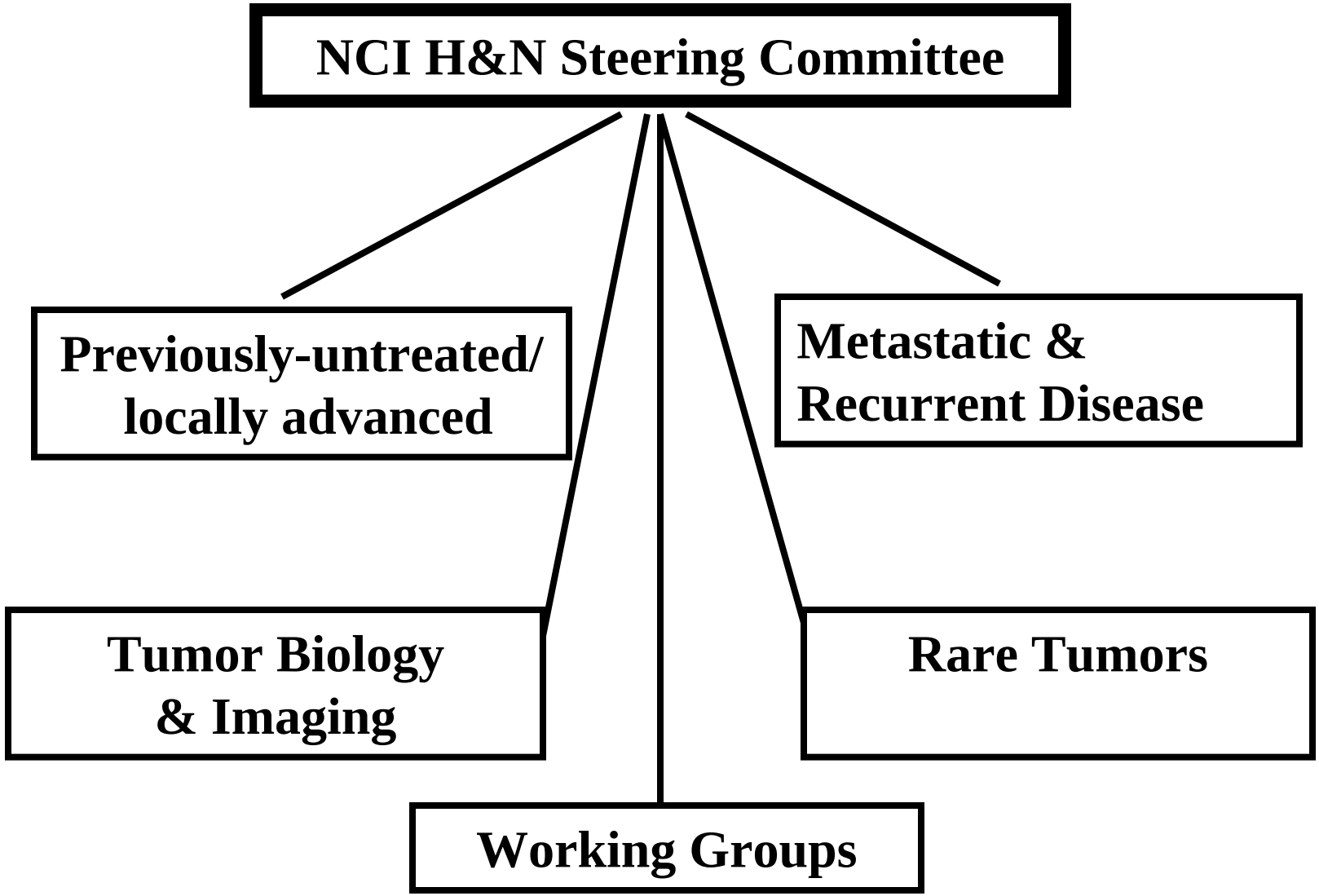
  ACRIN 6685: PET Staging in the N0 Neck

  in process

- H&N Clinical Trials Planning Meeting:

  HPV-related H&N Cancer, Wash DC, Nov 2008

Head and Neck Task Forces



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**

Concepts reviewed by HNSC in 2008

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

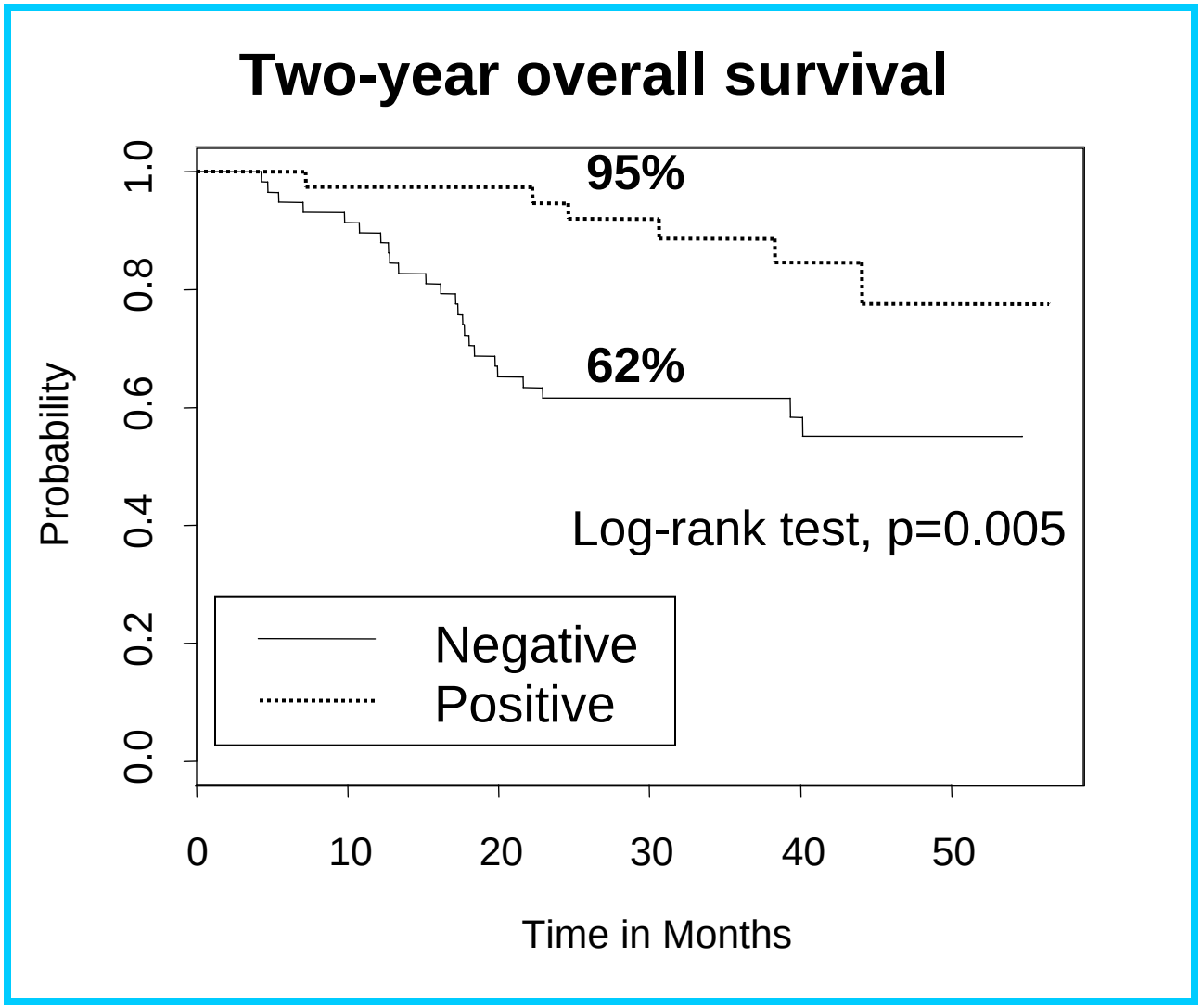
Proceedings to be published in Journal (Head and Neck)

Two distinct head and neck cancers

	HPV-positive	HPV-negative
Anatomic site	Tonsil / BOT	All sites
Histology	Basaloid	Keratinized
Age	Younger	Older
Gender	3:1 men	3:1 men
SE status	High	Low
Risk factors	Sexual behavior	Alcohol / tobacco
Incidence	Increasing	Decreasing
Survival	Improved	Worse

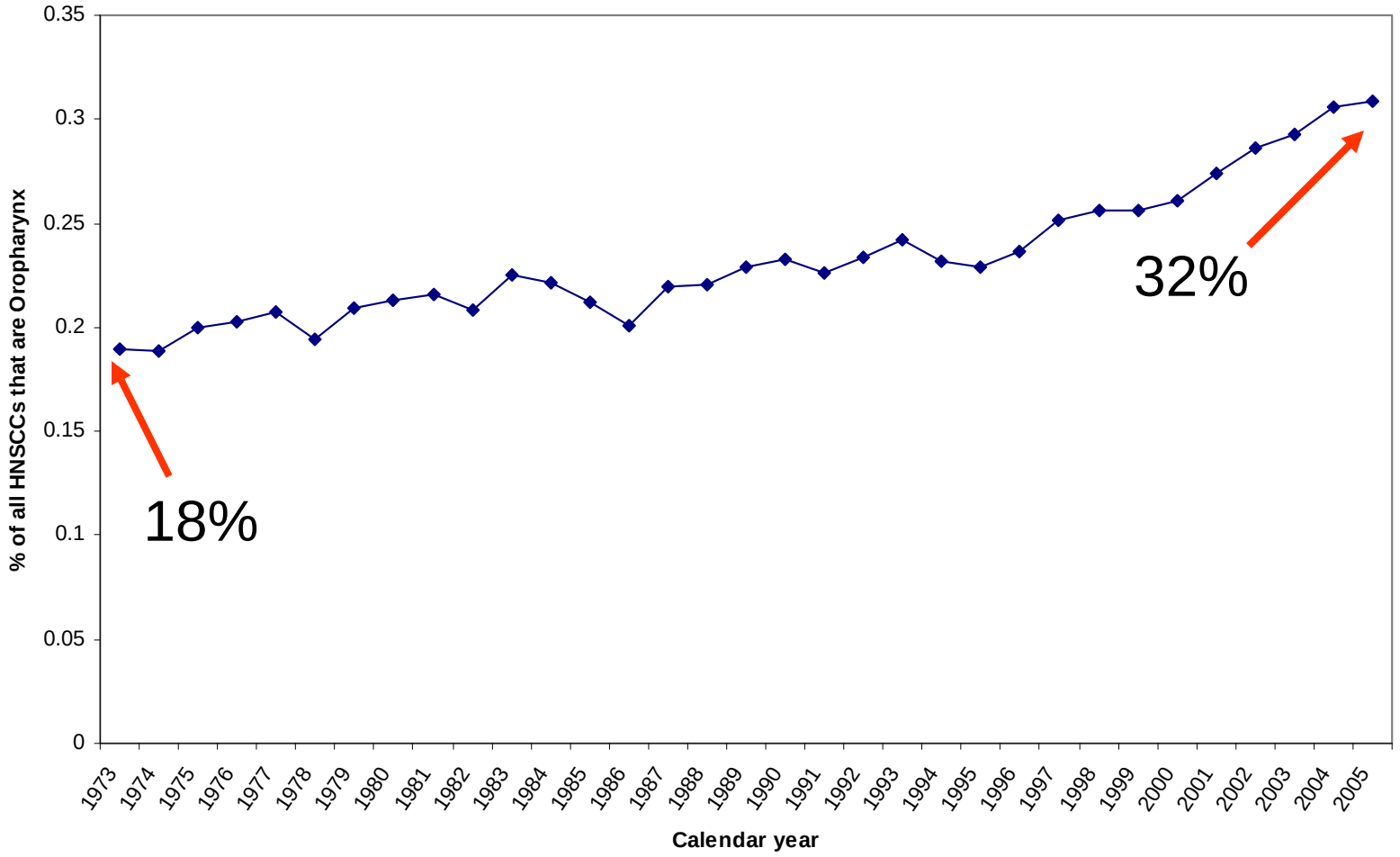
Adapted from M. Gillison

Tumor HPV status and survival



Fahkri 2008 JCO

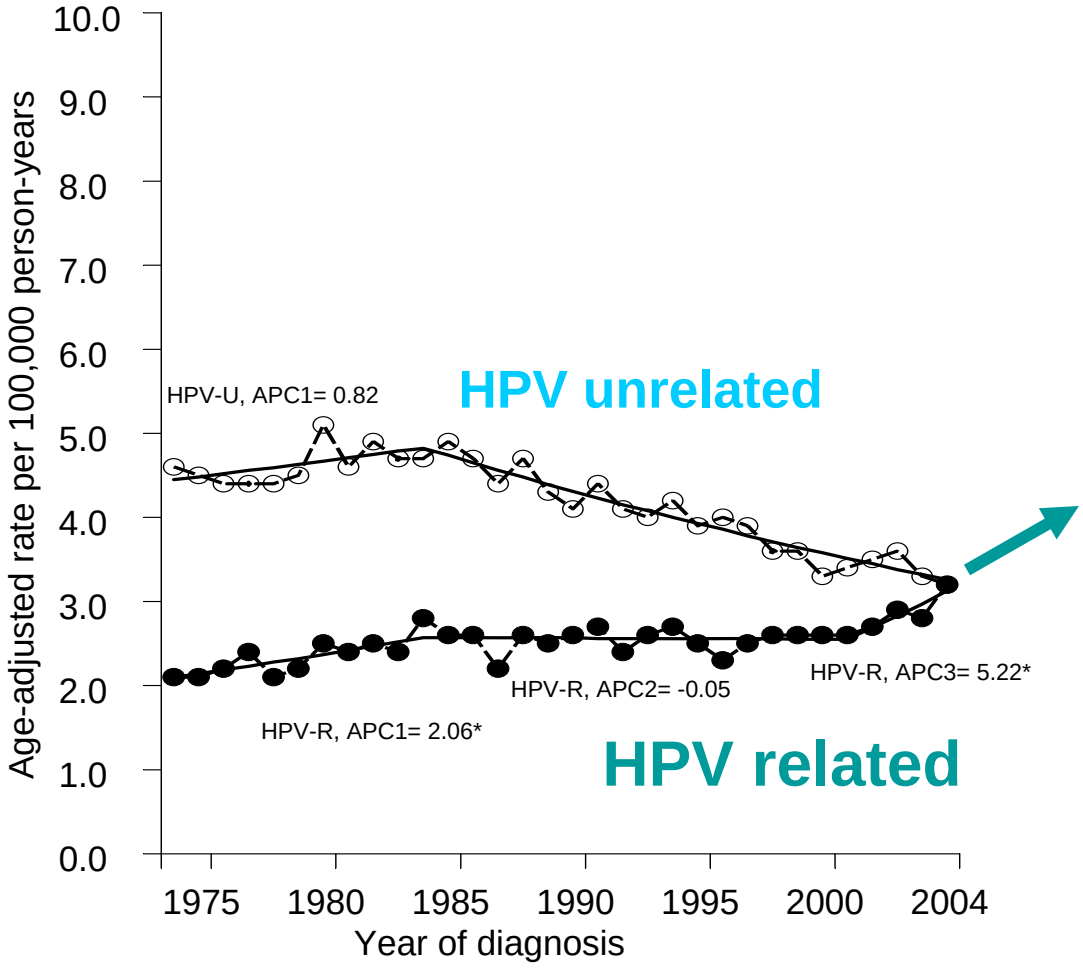
Proportion of all HNSCC that are oropharynx, U.S. 1973-2005



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

REGISTER

OPX HPV +

T2-4, N0-N3

→

Stratify by Smoking

Randomize

Reduced RT Dose (Standard Chemo)

vs

Reduced Chemo Intensity (Standard RT)

Vs

Reduced RT + Chemo Intensity

vs

RT 70 Gy + Concurrent Platinum (Standard of Care)

***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

Register	Stratify	Randomize
T2-3, N0-2 or T1, N1-2/M0 Oral cavity, oropharynx or larynx SCCA *Mandatory central Analysis of tumor tissue for EGFR and HPV*	EGFR expression HPV Status 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/m^2 RT, 2 Gy/day in 30 fractions for a total of 60 Gy plus Cetuximab: 250 mg/m^2/week x 6-7 weeks plus Cetuximab: 250 mg/m^2/week x 4 weeks post-RT for a total of 11-12 doses

RTOG 0811 cont'd

Primary objective: Efficacy, defined as overall survival

Secondary objectives: (summarized)

Acute/LateToxicity

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

Concepts reviewed by HNSC in 2008 cont'd

ACRIN 6685

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

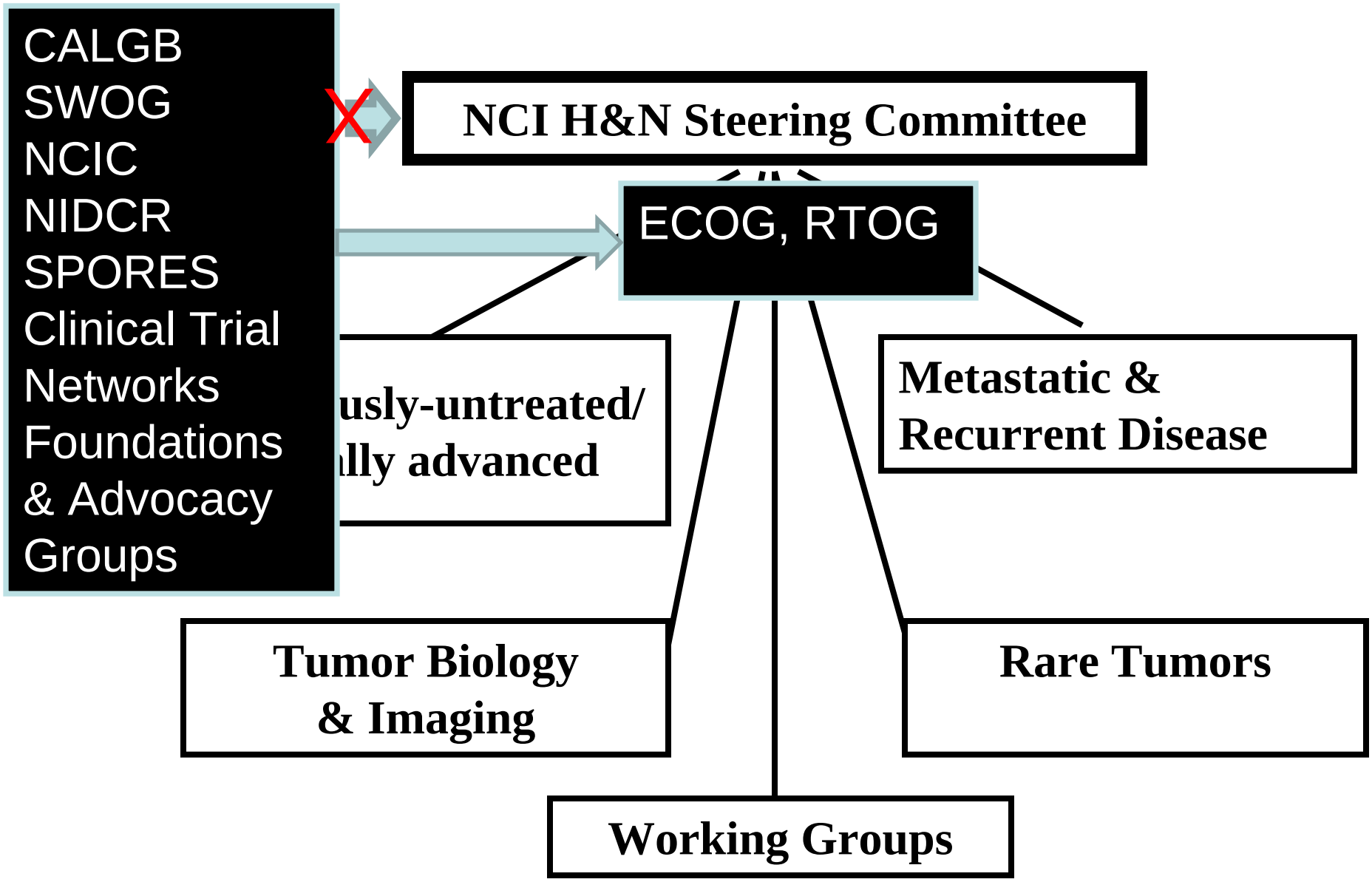
Opportunity to Accelerate Bench ⇄ Bedside Discovery

- 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



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

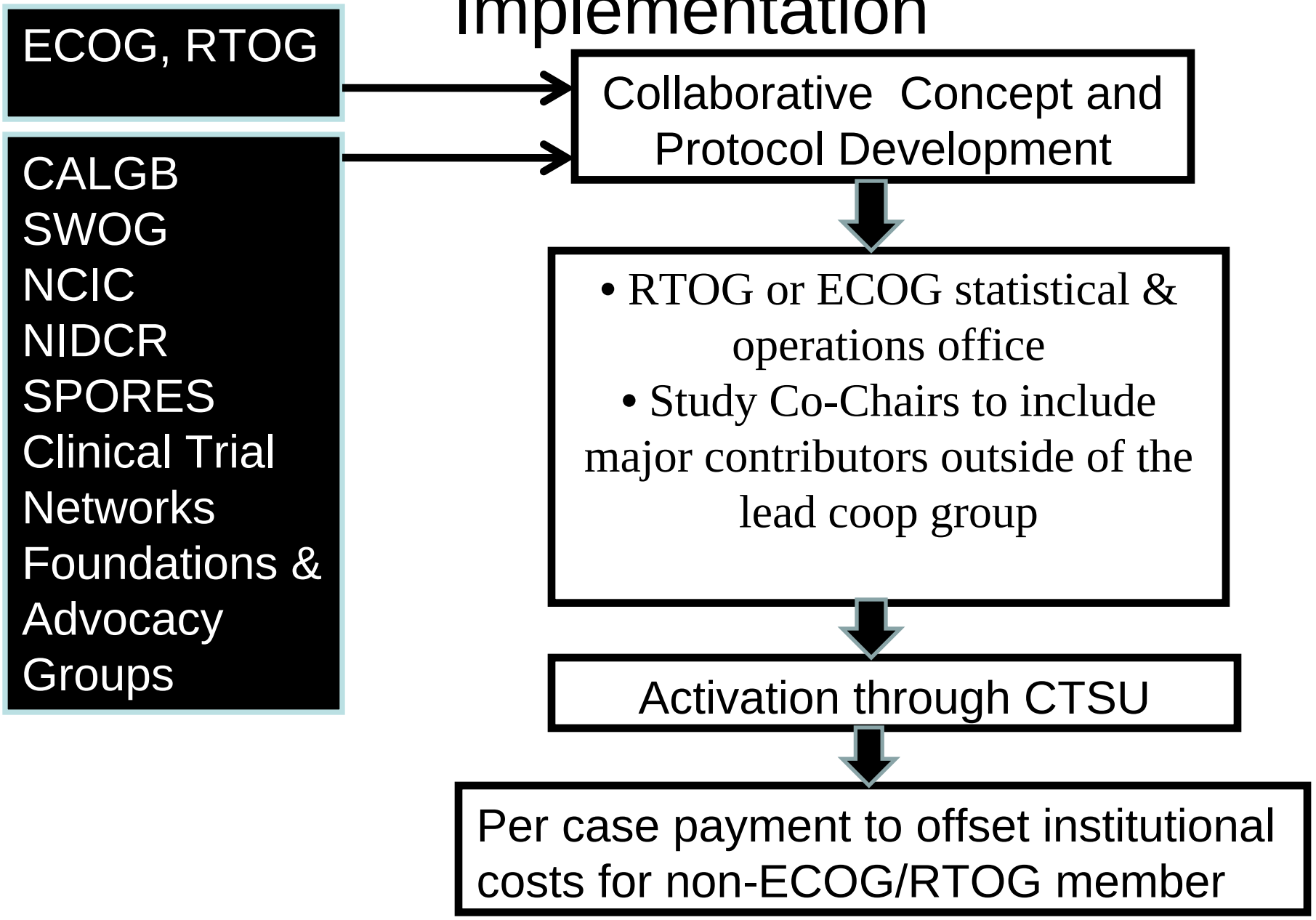
Head and Neck Cancer Leveraging Opportunities

- 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



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