The Integration and Impact of Modern Radiotherapy Techniques in Clinical Practice

Kian Ang

Funding: P01-CA06294, R01-CA84415, GF Fletcher Chair, Imclone (phase III trial)
From Bench to Bedside
Head and Neck Carcinoma

Track record in the development of:

- Altered fractionation regimens
- Concurrent radiation-chemotherapy
Biological Basis of Altered Fractionation

Hyperfractionation

Accelerated Fractionation

Thames et al., 1982

Differential Fractionation Effect

Withers et al., 1988

Clonogen Repopulation

Integration of lab research with clinical analyses
Supra-Additive Effect of RT + Cisplatin

Bartelink et al., 1986

Cisplatin

RT (4 Gy x 5) – if additive

Supra-Additive Observed

Cisplatin
Altered Fractionation & Radio-chemotherapy
Overall Survival

<table>
<thead>
<tr>
<th>Therapy Modality</th>
<th>Absolute benefit at 5 years*</th>
<th>Risk Reduction*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered Fractionation (N=6,515)¹</td>
<td>3.4 %</td>
<td>8 %</td>
<td>0.003</td>
</tr>
<tr>
<td>Hyperfractionation</td>
<td>8.2 %</td>
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<td>Accelerated Fx - ↓ Dose</td>
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<td>- ≅ Dose</td>
<td>2.0 %</td>
<td>3 %</td>
<td>(HF vs. AF)</td>
</tr>
<tr>
<td>Radio-chemotherapy (N=17,493)²</td>
<td>4.1 %</td>
<td>10 %</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>2.3 %</td>
<td>2 %</td>
<td>NS</td>
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<td>Cisplatin w/o FU (N=2,664)</td>
<td>9.6%</td>
<td>24%</td>
<td></td>
</tr>
</tbody>
</table>

*Relative to Conventional Radiotherapy

Efficacy ~ Toxicity of Radio-Chemotherapy

Subjects (%)

- RT alone (n=231)
- Combined RT + cisplatin (n=228)

p<0.001

Research Directions (M0 Patients)

Topographic Targeting: IMRT - IGRT

- Tumor Control
  - Biologic Targeting:
    - ✅ signaling pathway
    - ✅ pattern of relapse

- Toxicity
  - NT Protection & Symptom Management:
    - ✅ use of KGF
A method to shape dose distributions to target volumes with optimized non-uniform beam intensities
IMRT: Biologic Rationale

Multiple Portals
↓ Dose/F
(Outside GTV)

Isodose Shaping
↓ NT Volume in High-Dose Region

↑ NT Tolerance

↓ Toxicity (↑ QOL)

↑ Tumor Control

Therapy Intensification
IMRT for Head and Neck Cancer
MDACC

- Oropharyngeal carcinomas
- Nasopharyngeal carcinomas
  - Sinonasal cancers
- Thyroid neoplasms
IMRT for Oropharynx Cancer

- 2000-June 2004: 259 patients
- Age: 30-84 (54) years; 85% male
- Site: tonsil-49%; tongue base-43%
- T1-2(x): 220; T3-4: 39; N+: 225
- Chemotherapy: 62 (T3-4 or N2-3)
- 3-Y local control: 94%
- 3-Y overall survival: 88%

Garden et al., ASTRO 2006
Study population: 67 patients (14 centers)

- Tumor: tongue base-20 (39%), tonsil-33 (49%), soft palate 8 (12%)

- Stage: T1-25%, T2-75%; N0-57%, N1-43%

- Median follow-up: 1.6 (0.2-3.8) years

- LR progression: 3 patients (4.9%)

- No metastatic disease observed
Training & QA Procedures

Credentialing - H&N Atlas - Online Review

IMRT is integrated into ongoing & new protocols
IMRT ± Chemotherapy for NPC
Progression-Free: Local & Regional

5-Y nodal control: 97%
5-Y primary tumor control: 94%
5-Y metastasis-free: 66%

N = 87
Median FU = 30 months

Lee et al (UCSF), IJROBP, 53:1:12-21
Recovery of Saliva Flow (A vs C)

Kam et al., ASCO 2005 (NPC)

Fractional Change in Parotid Flow-rate vs Time Post Irradiation

- **IMRT**
- **Non-IMRT**

<table>
<thead>
<tr>
<th>Time Post RT</th>
<th>IMRT</th>
<th>Non-IMRT</th>
</tr>
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<tr>
<td>6 week</td>
<td>p &lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>6 month</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>0.0001</td>
<td></td>
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Adaptive Radiotherapy - Anatomic Changes
19 CT Scans over 47 Days

Patient Immobilized with Acquaplast Mask
CTs Aligned Using BBs on Mask

Barker et al. *IJROBP* 59:960-970, 2004 (MDACC); Lei Dong et al. (MDACC)
Dosimetric Impact of Anatomic Changes

Original Plan

Four Weeks Later (Mapped back to the original planning CT using deformable registration)

Lei Dong et al. (MDACC)
Targeted Therapy

Biologic Targeting
Perturbed Signaling Pathway

Topographic Targeting
IMRT

EGFR
EGFR vs Tumor Response (Rodent Models)

Akimoto et al., Clin Cancer Res, 1999

Single Dose

Tumor Cure Dose (Gy)

r=0.8, p<0.01

EGFR Densitometric Value
EGFR vs Radiosensitivity

Liang et al., IJROBP, 2003
EGFR Expression vs Survival

Overall Survival

Disease-Free Survival

p=0.0006

p=0.0016

n=155

n=155

Ang et al., Cancer Research 62: 7350, 2002
EGFR Expression vs Pattern of Failure

**Local-Regional Relapse**

- **p=0.003**
- **n=155**

**Distant Metastasis**

- **p=0.96**
- **n=155**

Ang et al., Cancer Research 62: 7350, 2002
Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck

James A. Bonner, M.D., Paul M. Harari, M.D., Jordi Giralt, M.D., Nozar Azarnia, Ph.D., Dong M. Shin, M.D., Roger B. Cohen, M.D., Christopher U. Jones, M.D., Ranjan Sur, M.D., Ph.D., David Raben, M.D., Jacek Jassem, M.D., Ph.D., Roger Ove, M.D., Ph.D., Merrill S. Kies, M.D., Jose Baselga, M.D., Hagop Youssoufian, M.D., Nadia Amellal, M.D., Eric K. Rowinsky, M.D., and K. Kian Ang, M.D., Ph.D.*
A Phase III Study of Radiotherapy ± Cetuximab (C225) in Patients with Locally Advanced HNSCC

Local-Regional Control

HR: 0.68 (0.52 - 0.89)

Survival

HR = 0.74 (0.57 - 0.97)

No impact on DM

Bonner et al., NEJM, 2006
### A Phase III Study of Radiotherapy ± Cetuximab in Patients with Locally Advanced SCCHN

<table>
<thead>
<tr>
<th>% Toxicity</th>
<th>RT (N=212)</th>
<th></th>
<th>RT+C (N=208)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Gr.</td>
<td>Gr. 3/4</td>
<td>All Gr.</td>
<td>Gr. 3/4</td>
</tr>
<tr>
<td>Mucositis/Stomatitis</td>
<td>93</td>
<td>52</td>
<td>91</td>
<td>54</td>
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<tr>
<td>Dysphagia</td>
<td>63</td>
<td>30</td>
<td>64</td>
<td>25</td>
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<tr>
<td>Xerostomia</td>
<td>70</td>
<td>3</td>
<td>64</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue/Malaise</td>
<td>50</td>
<td>5</td>
<td>52</td>
<td>4</td>
</tr>
<tr>
<td>Radiation Dermatitis</td>
<td>90</td>
<td>18</td>
<td>85</td>
<td>23</td>
</tr>
<tr>
<td>Skin reaction</td>
<td>91</td>
<td>18</td>
<td>97*</td>
<td>34**</td>
</tr>
<tr>
<td>Infusion reaction#</td>
<td>2</td>
<td>–</td>
<td>14**</td>
<td>3*</td>
</tr>
</tbody>
</table>

*p < 0.05, ** p < 0.001, Fisher’s exact test. # Listed as related to cetuximab
Lessons

● **Excitement:** validation of the concept that targeting a perturbed signaling pathway can selectively sensitize tumor to RT

● **Clinical challenges:**
  - Cetuximab benefits 10-15% of patients
  - LR relapse still occurs in >50% of patients
  - **Integrate cetuximab with RT + chemotherapy**
  - Interpret findings in broad clinical context
Integrating Cetuximab with RT+Chemotherapy
RTOG Phase III Trial (0522), PI: K. Ang, N: 720

Stage III & IV* SCC of:
- Oropharynx
- Hypopharynx
- Larynx

Stratify:
- Larynx ~ Others
- N0~N1,2a,2b~N2c-3
- KPS
  - 60-80 ~ 90-100
- 3-D vs IMRT
- Pre-Rx PET (yes/no)

*Exclude T1 any N or T2N1

1. Accelerated FX* +
   CDDP: 100 mg/m², q3W X 2

2. Accelerated FX* +
   CDDP: 100 mg/m², q3W X 2
   C225: 400 mg/m², Pre-RT, then
   250 mg/m²/w x 7
RTOG H-0234: Locally Advanced Resected
Randomized Phase II, PI: P. Harari, N: >240

Surgical Resection

High Risk

3-D vs IMRT

RT → RT + C225 (400 → 250 mg/m², qW)
+ DDP (30 mg/m², qW)

RT → RT + C225 (400 → 250 mg/m², qW)
+ Docetaxel (15 mg/m², qW)

Days after Radiation

Tumor Size (mm)

Control

10 Gy
+ Doc

10 Gy
+ C225

10 Gy
+ C225
+ Doc

A431

Days after Radiation
Research Directions (M0 Patients)

Topographic Targeting: IMRT - IGRT

↑ Tumor Control

✓ Biologic Targeting:
  ✓ signaling pathway
  ✓ pattern of relapse

↓ Toxicity

✓ NT Protection & Symptom Management:
  ✓ use of KGF
## IMRT ± Chemotherapy for NPC

<table>
<thead>
<tr>
<th>Center</th>
<th>N</th>
<th>Stage</th>
<th>FU (mo)</th>
<th>LC</th>
<th>DM-Free</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bucci</strong></td>
<td>118</td>
<td>50% T3-4</td>
<td>30</td>
<td>96%</td>
<td>72%</td>
</tr>
<tr>
<td>IJROBP, 2004</td>
<td></td>
<td></td>
<td></td>
<td>(4-year data)</td>
<td></td>
</tr>
<tr>
<td><strong>Kam</strong></td>
<td>63</td>
<td>51% T3-4</td>
<td>29</td>
<td>92%</td>
<td>79%</td>
</tr>
<tr>
<td>IJROBP, 2004</td>
<td></td>
<td></td>
<td></td>
<td>(3-year data)</td>
<td></td>
</tr>
<tr>
<td><strong>Wolden</strong></td>
<td>74</td>
<td>51% T3-4</td>
<td>35</td>
<td>91%</td>
<td>78%</td>
</tr>
<tr>
<td>IJROBP, 2005</td>
<td></td>
<td></td>
<td></td>
<td>(3-year data)</td>
<td></td>
</tr>
</tbody>
</table>
## RCTs Bevacizumab + Chemotherapy

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>BV dose</th>
<th># Pts.</th>
<th>Response Rate (%)</th>
<th>m-PFS (months)</th>
<th>m-OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>CT</td>
<td>CT + BV</td>
<td>CT</td>
</tr>
<tr>
<td>Colorectal</td>
<td>5 mg/kg</td>
<td>813</td>
<td>34.8</td>
<td>44.8</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>q2w</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSCLC</td>
<td>15 mg/kg</td>
<td>878</td>
<td>10</td>
<td>27</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>q3w</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>15 mg/kg</td>
<td>715</td>
<td>14.2</td>
<td>28.2</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>q2w</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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NPC – RTOG 0615 (Phase II, PI: N. Lee)

**Concurrent:**
- IMRT (70 Gy)
- CDDP (100 mg/m²) x 3 cycles q 3 W
- BV 15 mg/kg q 3 W

**Adjuvant:**
- CDDP (80 mg/m²)
- 5FU (1000 mg/m²) x 3 cycles q 3 W
- BV 15 mg/kg q 3 W

T ≥ 2b or N+

Type: WHO I-III
PORT ± Cisplatin for HNC Patients with ECE and/or Margin+

RTOG 9501\(^*\)

- RT Alone: Yellow line
- RT+DDP: Black line

EORTC 22931\(^*\)

- RT Alone: Yellow line
- RT+DDP: Black line

\(p = 0.063\)

\(p = 0.019\)

\(^*\)Cooper et al., NEJM, 2004; \(^*\)Bernier et al., NEJM, 2004; Bernier et al., Head Neck, 2005
PoRT for H & N CANCER: Survival vs Risk Grouping

Ang, Trotti, Brown et al., IJROBP, 2001
ZD6474: A Oral Dual EGFR-VEGFR TKI

Effect of ZD6474 and RT on Lung Adenocarcinoma

Rt

Lt

CONTROL

RT

ZD6474

ZD6474 + RT

Courtesy: M. O’Reilly
**RT ± Paclitaxel (PTX) or ZD6474**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>XRT</th>
<th>Paclitaxel</th>
<th>RT+PTX</th>
<th>ZD6474</th>
<th>RT+ZD6474</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGF</strong></td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
</tr>
<tr>
<td><strong>EGFR</strong></td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
<td><img src="image9" alt="Image" /></td>
<td><img src="image10" alt="Image" /></td>
<td><img src="image11" alt="Image" /></td>
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</tr>
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<td><strong>VEGF</strong></td>
<td><img src="image13" alt="Image" /></td>
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<td><img src="image16" alt="Image" /></td>
<td><img src="image17" alt="Image" /></td>
<td><img src="image18" alt="Image" /></td>
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<tr>
<td><strong>VEGFR2</strong></td>
<td><img src="image19" alt="Image" /></td>
<td><img src="image20" alt="Image" /></td>
<td><img src="image21" alt="Image" /></td>
<td><img src="image22" alt="Image" /></td>
<td><img src="image23" alt="Image" /></td>
<td><img src="image24" alt="Image" /></td>
</tr>
<tr>
<td><strong>pEGFR + CD31</strong></td>
<td><img src="image25" alt="Image" /></td>
<td><img src="image26" alt="Image" /></td>
<td><img src="image27" alt="Image" /></td>
<td><img src="image28" alt="Image" /></td>
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<td><img src="image35" alt="Image" /></td>
<td><img src="image36" alt="Image" /></td>
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RTOG 0619: Post-op Adjuvant
Phase II(R) in Planning, PI: David Raben

Surgical Resection

High Risk

RANDOMIZE

RT + DDP (30 mg/m², qW)

RT + DDP (30 mg/m², qW) + ZD6474 (300 mg daily)
Research Directions

Topographic Targeting: IMRT - IGRT

↑ Tumor Control

Biologic Targeting:
✓ signaling pathway
✓ pattern of relapse

↓ Toxicty

Normal Tissue Protection:
✓ use of growth factors
Grade 4 Mucositis
KGF – Palifermin (Kepivance®)

- FGF family (FGF-7) paracrine effector
- Binds to KGFR, only on epithelial cells
- Specific stimulatory activity for epithelial cells (unlike other FGFs)
  - proliferation
  - differentiation
  - survival
- Rhu-KGF: N-terminal truncated version of endogenous KGF to improve stability
- Water-soluble 16.3 kDa protein
- Produced in E. coli

FGF: Fibroblast growth factor.
Palifermin - biological activity in human buccal mucosa

Pre-palifermin H&E

24 hr post-palifermin (40 µg/kg/day for 3 days) H&E

H&E = hematoxylin and eosin
Effect of Palifermin (rHuKGF) on Mucositis Patients Undergoing TBI + CTH + AuBMT (Phase III)

Placebo

Palifermin

Placebo

Palifermin

= single IV dose of study drug (60 mcg/kg/d palifermin or placebo)

VP-16: 60 mg/kg

12 Gy in 3-4 days

Cyclophosphamide: 100 mg/kg

Autologous PBPC infusion

G-CSF until engraftment

End of study

Randomization

Day

-11

-8

-4

-2

0

28

PBPC: Peripheral blood progenitor cell. Stratification by center and hematologic malignancy type

Adapted from Spielberger R, NEJM 351:2590-2598, 2004
Effect of Palifermin (rHuKGF) on Mucositis
Patients Undergoing TBI + CTH + AuBMT (Phase III)

Grade 4 Mucositis

<table>
<thead>
<tr>
<th>Incidence (%)</th>
<th>Placebo (n = 106)</th>
<th>Palifermin (n = 106)</th>
<th>p &lt; 0.001</th>
</tr>
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<tbody>
<tr>
<td>62%</td>
<td></td>
<td>20%</td>
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Mean Duration (Days)

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<td>6.7d (5.3, 8.0)</td>
<td>3.7</td>
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p < 0.001

Adapted from Spielberger R, NEJM 351:2590-2598, 2004
RTOG 0435: KGF in Reducing Mucositis Phase III Trial, PI: D. Rosenthal

**Screening**

**Randomization**

- RT x 70Gy/7 weeks*
- CDDP 100 mg/m² x 3

If ulcerative OM at week 7

**Palifermin**

**Placebo**

Study Duration: Assess 2x/w during & after RT until mucositis resolves to WHO ≤ grade 1 or 8 weeks after RT

*IMRT or 3D-RT allowed
Summary - Opportunities & Challenges

- Significant progress in H&N oncology
- Optimize precision radiotherapy
- Develop novel combined therapy by
  - perturbed signaling pathway (EGFR) – validated the proof of principle
  - relapse pattern - ongoing
  - individual tumor features – high priority
- Find strategy to reduce mucositis
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Supra-Additive Effect of RT + Cisplatin

Bartelink et al., 1986

RT (4 Gy x 5) – if additive

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Supra-Additive Observed
# Altered Fractionation & Radio-chemotherapy

## Overall Survival

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\(^1\)Bourhis et al., Lancet 2006; \(^2\)Pignon & Bourhis, Multidiscipl. H&N Meeting, 2007
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperfractionation</td>
<td>8.2 %</td>
<td>22 %</td>
<td>0.02</td>
</tr>
<tr>
<td>Accelerated Fx -  Dose</td>
<td>1.7 %</td>
<td>6 %</td>
<td></td>
</tr>
<tr>
<td>-  Dose</td>
<td>2.0 %</td>
<td>3 %</td>
<td></td>
</tr>
<tr>
<td>Radio-chemotherapy (N=17,493)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>2.3 %</td>
<td>2 %</td>
<td>NS</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>2.2 %</td>
<td>5 %</td>
<td>NS</td>
</tr>
<tr>
<td>Concurrent</td>
<td>6.9 %</td>
<td>19 %</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Cisplatin w/o FU (N=2,664)</td>
<td>9.6%</td>
<td>24%</td>
<td></td>
</tr>
</tbody>
</table>

*Relative to Conventional Radiotherapy

Efficacy ~ Toxicity of Radio-Chemotherapy

Research Directions (M0 Patients)

Topographic Targeting: IMRT - IGRT

- Tumor Control
  - Biologic Targeting: 
    - signaling pathway
    - pattern of relapse

- Toxicity
  - NT Protection & Symptom Management: 
    - use of KGF
A method to shape dose distributions to target volumes with optimized non-uniform beam intensities
IMRT: Biologic Rationale

Multiple Portals
↓ Dose/F
(Outside GTV)

Isodose Shaping
↓ NT Volume in High-Dose Region

↑ NT Tolerance

↓ Toxicity (↑ QOL)

↑ Tumor Control

Therapy Intensification
IMRT for Head and Neck Cancer

MDACC

- Oropharyngeal carcinomas
- Nasopharyngeal carcinomas
  - Sinonasal cancers
  - Thyroid neoplasms
IMRT for Oropharynx Cancer

- 2000-June 2004: 259 patients
- Age: 30-84 (54) years; 85% male
- Site: tonsil-49%; tongue base-43%
- T1-2(x): 220; T3-4: 39; N+: 225
- Chemotherapy: 62 (T3-4 or N2-3)
- 3-Y local control: 94%
- 3-Y overall survival: 88%
Study population: 67 patients (14 centers)

Tumor: tongue base-20 (39%), tonsil-33 (49%), soft palate 8 (12%)

Stage: T1-25%, T2-75%; N0-57%, N1-43%

Median follow-up: 1.6 (0.2-3.8) years

LR progression: 3 patients (4.9%)

No metastatic disease observed
Training & QA Procedures

Credentialing - H&N Atlas - Online Review

IMRT is integrated into ongoing & new protocols
IMRT ± Chemotherapy for NPC Progression-Free: Local & Regional

5-Y nodal control: 97%
5-Y primary tumor control: 94%
5-Y metastasis-free: 66%

N= 87
Median FU=30 months

Lee et al (UCSF), IJROBP, 53:1:12-21
Recovery of Saliva Flow (A vs C)

Kam et al., ASCO 2005 (NPC)

Impact on QOL parameters was less obvious

Fractional Change in Parotid Flow-rate vs Time Post Irradiation

IMRT vs Non-IMRT

Time Post RT

6 week
6 month
1 year

Ratio of post RT/pre-RT Parotid outflow

p < 0.0001
0.0001
0.0001
Adaptive Radiotherapy - Anatomic Changes
19 CT Scans over 47 Days

Patient Immobilized with Acquaplast Mask
CTs Aligned Using BBs on Mask

Barker et al. *IJROBP* 59:960-970, 2004 (MDACC); Lei Dong et al. (MDACC)
Dosimetric Impact of Anatomic Changes

Original Plan

Four Weeks Later (Mapped back to the original planning CT using deformable registration)

Lei Dong et al. (MDACC)
Targeted Therapy

Biologic Targeting
Perturbed Signaling Pathway

Topographic Targeting
IMRT

EGFR
EGFR vs Tumor Response (Rodent Models)

Akimoto et al., Clin Cancer Res, 1999

Single Dose

r=0.8, p<0.01

EGFR Densitometric Value
EGFR vs Radiosensitivity

Liang et al., IJROBP, 2003
EGFR Expression vs Survival

Overall Survival

Disease-Free Survival

Ang et al., Cancer Research 62: 7350, 2002
EGFR Expression vs Pattern of Failure

Local-Regional Relapse

- EGFR > Median
  - % Failed: 0 to 100
  - Years from Randomization: 0 to 5
- EGFR ≤ Median
  - % Failed: 0 to 100
  - Years from Randomization: 0 to 5

p = 0.003
n = 155

Distant Metastasis

- EGFR > Median
  - % with Mets: 0 to 100
  - Years from Randomization: 0 to 5
- EGFR ≤ Median
  - % with Mets: 0 to 100
  - Years from Randomization: 0 to 5

p = 0.96
n = 155

Ang et al., Cancer Research 62: 7350, 2002
A Phase III Study of High Dose Radiotherapy ± Cetuximab (C225)

Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck

James A. Bonner, M.D., Paul M. Harari, M.D., Jordi Giralt, M.D., Nozar Azarnia, Ph.D., Dong M. Shin, M.D., Roger B. Cohen, M.D., Christopher U. Jones, M.D., Ranjan Sur, M.D., Ph.D., David Raben, M.D., Jacek Jassem, M.D., Ph.D., Roger Ove, M.D., Ph.D., Merrill S. Kies, M.D., Jose Baselga, M.D., Hagop Youssoufian, M.D., Nadia Amellal, M.D., Eric K. Rowinsky, M.D., and K. Kian Ang, M.D., Ph.D.*
A Phase III Study of Radiotherapy ± Cetuximab (C225) in Patients with Locally Advanced HNSCC

Local-Regional Control

HR: 0.68 (0.52 - 0.89)

- RT: 213 patients, median 15 m, 1-Year 55%, 2-Year 41%, Log rank p= 0.005
- RT+C: 211 patients, median 24 m, 1-Year 63%, 2-Year 50%

Survival

HR = 0.74 (0.57 - 0.97)

- RT: 213 patients, median 29 m, 1-Year 55%, 2-Year 45%, Log rank p= 0.005
- RT+C: 211 patients, median 49 m, 1-Year 62%, 2-Year 56%

No impact on DM

Bonner et al., NEJM, 2006
A Phase III Study of Radiotherapy ± Cetuximab in Patients with Locally Advanced SCCHN

<table>
<thead>
<tr>
<th>% Toxicity</th>
<th>RT (N=212)</th>
<th>RT+C (N=208)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Gr.</td>
<td>Gr. 3/4</td>
</tr>
<tr>
<td>Mucositis/Stomatitis</td>
<td>93</td>
<td>52</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>63</td>
<td>30</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>70</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue/Malaise</td>
<td>50</td>
<td>5</td>
</tr>
<tr>
<td>Radiation Dermatitis</td>
<td>90</td>
<td>18</td>
</tr>
<tr>
<td>Skin reaction</td>
<td>91</td>
<td>18</td>
</tr>
<tr>
<td>Infusion reaction#</td>
<td>2</td>
<td>–</td>
</tr>
</tbody>
</table>

*p < 0.05, ** p < 0.001, Fisher’s exact test. # Listed as related to cetuximab
Lessons

● **Excitement:** validation of the concept that targeting a perturbed signaling pathway can selectively sensitize tumor to RT

● **Clinical challenges:**
  - Cetuximab benefits 10-15% of patients
  - LR relapse still occurs in >50% of patients
  - Integrate cetuximab with RT + chemotherapy
  - Interpret findings in broad clinical context
Stage III & IV* SCC of:
- Oropharynx
- Hypopharynx
- Larynx

Stratify:
- Larynx ~ Others
- N0~N1,2a,2b~N2c-3
- KPS
  - 60-80 ~ 90-100
- 3-D vs IMRT
- Pre-Rx PET (yes/no)

*Exclude T1 any N or T2N1

1. Accelerated FX* + CDDP: 100 mg/m², q3W X 2

2. Accelerated FX* + CDDP: 100 mg/m², q3W X 2
   C225: 400 mg/m², Pre-RT, then 250 mg/m²/w x 7

Integrating Cetuximab with RT+Chemotherapy
RTOG Phase III Trial (0522), PI: K. Ang, N: 720
RTOG H-0234: Locally Advanced Resected
Randomized Phase II, PI: P. Harari, N: >240

Surgical Resection

High Risk

3-D vs IMRT

RT + C225 (400 → 250 mg/m$^2$, qW)
+ DDP (30 mg/m$^2$, qW)

RT + C225 (400 → 250 mg/m$^2$, qW)
+ Docetaxel (15 mg/m$^2$, qW)
Research Directions (M0 Patients)

**Topographic Targeting:**
- IMRT - IGRT

**Biologic Targeting:**
- ✅ signaling pathway
- ✅ pattern of relapse

**NT Protection & Symptom Management:**
- ✅ use of KGF

**Tumor Control**

**Toxicity**
## IMRT ± Chemotherapy for NPC

<table>
<thead>
<tr>
<th>Center</th>
<th>N</th>
<th>Stage</th>
<th>FU (mo)</th>
<th>LC</th>
<th>DM-Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bucci, IJROBP, 2004(abs)</td>
<td>118</td>
<td>50% T3-4</td>
<td>30</td>
<td>96%</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(4-year data)</td>
</tr>
<tr>
<td>Kam, IJROBP, 2004</td>
<td>63</td>
<td>51% T3-4</td>
<td>29</td>
<td>92%</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(3-year data)</td>
</tr>
<tr>
<td>Wolden, IJROBP, 2005</td>
<td>74</td>
<td>51% T3-4</td>
<td>35</td>
<td>91%</td>
<td>78%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(3-year data)</td>
</tr>
</tbody>
</table>
### RCTs Bevacizumab + Chemotherapy

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>BV dose</th>
<th># Pts.</th>
<th>Response Rate (%)</th>
<th>m-PFS (months)</th>
<th>m-OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(CT)</td>
<td>(CT + BV)</td>
<td>(CT)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>5 mg/kg</td>
<td>813</td>
<td>34.8</td>
<td>44.8</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>q2w</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSCLC</td>
<td>15 mg/kg</td>
<td>878</td>
<td>10</td>
<td>27</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>q3w</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>15 mg/kg</td>
<td>715</td>
<td>14.2</td>
<td>28.2</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>q2w</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hurwitz NEJM 2004; Sandler ASCO 2005; Miller ASCO 2005
NPC – RTOG 0615 (Phase II, PI: N. Lee)

**T≥2b or N+**

**Type: WHO I-III**

**Concurrent:**
- IMRT (70 Gy)
- CDDP (100mg/m²) x 3 cycles q 3 W
- BV 15mg/kg q 3W

**Adjuvant:**
- CDDP (80 mg/m²)
- 5FU (1000 mg/m²) x 3 cycles q 3W
- BV 15mg/kg q3W
PORT ± Cisplatin for HNC
Patients with ECE and/or Margin+

+Cooper et al., NEJM, 2004; *Bernier et al., NEJM, 2004; Bernier et al., Head Neck, 2005
PoRT for H & N CANCER: Survival vs Risk Grouping

Ang, Trotti, Brown et al., IJROBP, 2001
ZD6474: A Oral Dual EGFR-VEGFR TKI

Effect of ZD6474 and RT on Lung Adenocarcinoma

Courtesy: M. O’Reilly
<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>XRT</th>
<th>Paclitaxel</th>
<th>RT+PTX</th>
<th>ZD6474</th>
<th>RT+ZD6474</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGF</td>
<td><img src="image1.jpg" alt="Image" /></td>
<td><img src="image2.jpg" alt="Image" /></td>
<td><img src="image3.jpg" alt="Image" /></td>
<td><img src="image4.jpg" alt="Image" /></td>
<td><img src="image5.jpg" alt="Image" /></td>
<td><img src="image6.jpg" alt="Image" /></td>
</tr>
<tr>
<td>EGFR</td>
<td><img src="image7.jpg" alt="Image" /></td>
<td><img src="image8.jpg" alt="Image" /></td>
<td><img src="image9.jpg" alt="Image" /></td>
<td><img src="image10.jpg" alt="Image" /></td>
<td><img src="image11.jpg" alt="Image" /></td>
<td><img src="image12.jpg" alt="Image" /></td>
</tr>
<tr>
<td>VEGF</td>
<td><img src="image13.jpg" alt="Image" /></td>
<td><img src="image14.jpg" alt="Image" /></td>
<td><img src="image15.jpg" alt="Image" /></td>
<td><img src="image16.jpg" alt="Image" /></td>
<td><img src="image17.jpg" alt="Image" /></td>
<td><img src="image18.jpg" alt="Image" /></td>
</tr>
<tr>
<td>VEGFR2</td>
<td><img src="image19.jpg" alt="Image" /></td>
<td><img src="image20.jpg" alt="Image" /></td>
<td><img src="image21.jpg" alt="Image" /></td>
<td><img src="image22.jpg" alt="Image" /></td>
<td><img src="image23.jpg" alt="Image" /></td>
<td><img src="image24.jpg" alt="Image" /></td>
</tr>
<tr>
<td>pEGFR +CD31</td>
<td><img src="image25.jpg" alt="Image" /></td>
<td><img src="image26.jpg" alt="Image" /></td>
<td><img src="image27.jpg" alt="Image" /></td>
<td><img src="image28.jpg" alt="Image" /></td>
<td><img src="image29.jpg" alt="Image" /></td>
<td><img src="image30.jpg" alt="Image" /></td>
</tr>
<tr>
<td>pVEGFR2 +CD31</td>
<td><img src="image31.jpg" alt="Image" /></td>
<td><img src="image32.jpg" alt="Image" /></td>
<td><img src="image33.jpg" alt="Image" /></td>
<td><img src="image34.jpg" alt="Image" /></td>
<td><img src="image35.jpg" alt="Image" /></td>
<td><img src="image36.jpg" alt="Image" /></td>
</tr>
</tbody>
</table>
RTOG 0619: Post-op Adjuvant Phase II(R) in Planning, PI: David Raben

**Surgical Resection**

**Randomize**

RT + DDP (30 mg/m², qW)

**High Risk**

Randomize

RT + DDP (30 mg/m², qW) + ZD6474 (300 mg daily)
Research Directions

Topographic Targeting:
IMRT - IGRT

Tumor Control

Biologic Targeting:
✓ signaling pathway
✓ pattern of relapse

Toxicity

Normal Tissue Protection:
✓ use of growth factors
Grade 4 Mucositis
KGF – Palifermin (Kepivance®)

- FGF family (FGF-7) paracrine effector
- Binds to KGFR, only on epithelial cells
- Specific stimulatory activity for epithelial cells (unlike other FGFs)
  ✓ proliferation
  ✓ differentiation
  ✓ survival

- Rhu-KGF: N-terminal truncated version of endogenous KGF to improve stability
- Water-soluble 16.3 kDa protein
- Produced in E. coli

FGF: Fibroblast growth factor.
Palifermin - biological activity in human buccal mucosa

Pre-palifermin H&E

24 hr post-palifermin (40 µg/kg/day for 3 days) H&E

H&E = hematoxylin and eosin
Effect of Palifermin (rHuKGF) on Mucositis
Patients Undergoing TBI + CTH + AuBMT (Phase III)

Grade 4 Mucositis

<table>
<thead>
<tr>
<th>Incidence (%)</th>
<th>Placebo (n = 106)</th>
<th>Palifermin (n = 106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>62%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( p < 0.001 \)

<table>
<thead>
<tr>
<th>Mean Duration (Days)</th>
<th>Placebo (n = 106)</th>
<th>Palifermin (n = 106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.4</td>
<td>( p &lt; 0.001 )</td>
<td>3.7</td>
</tr>
</tbody>
</table>

\( 95\% \) CI: 6.7d (5.3, 8.0)

Adapted from Spielberger R, NEJM 351:2590-2598, 2004
RTOG 0435: KGF in Reducing Mucositis Phase III Trial, PI: D. Rosenthal

**Screening** → **Randomization**

- **RT x 70Gy/7 weeks***
- **CDDP 100 mg/m² x 3**

**If ulcerative OM at week 7**

**Palifermin** → **Placebo**

Study Duration: Assess 2x/w during & after RT until mucositis resolves to WHO ≤ grade 1 or 8 weeks after RT

*IMRT or 3D-RT allowed
Summary - Opportunities & Challenges

- Significant progress in H&N oncology
- Optimize precision radiotherapy
- Develop novel combined therapy by
  - perturbed signaling pathway (EGFR) – validated the proof of principle
  - relapse pattern - ongoing
  - individual tumor features – high priority
- Find strategy to reduce mucositis