Therapy of Locally Advanced Head and Neck Cancer: State of the Art

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Therapy of Locally Advanced SCCHN: State-of-the-Art

Dr. Burtness has the following relevant financial relationships with commercial interests to disclose:

• Grant/Research Support: Caris, Genentech, Millenium, Novartis, and Pfizer

• Consultant: Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, and Pfizer
Locally Advanced Disease

- Chemoradiation
- HPV Associated Disease
  - Treatment Deintensification is Not Standard
  - E1308
  - E1016
- HPV Negative Disease
- Is There an Intermediate Risk Cohort?
- How Does Minimally Invasive Surgery Contribute?
Chemoradiation

• Negative Studies of
  – Accelerated fractionation with CDDP
  – Tirapazamine
  – Cetuximab

• Trial Designs Compromised by Low Event Rate/High HPV Prevalence

• Standard of Care Unchanged
Key eligibility criteria:
• Stage III or IV (except T1 N+ and T2 N1) SCC of oral cavity, oropharynx, larynx, or hypopharynx

Stratification factors:
• Tumor site (larynx vs. non-larynx)
• Nodal stage (N0 vs. N+)
• Karnofsky PS (60-80 vs. 90-100)

Primary endpoint: overall survival HR (AFX-CB vs. SFX) 0.90 [0.72-1.13]; P = .18
Secondary endpoints:
– Progression-free survival HR 1.00 [0.81-1.23]; P = .50
– Local regional failure HR 1.11 [0.85-1.44]; P = .80
– Distant metastasis HR 0.81 [0.54-1.22]; P = .14

Ang K., et al. *NEJM* 2010;10.1056
Survival of R0129 Patients with Oropharyngeal Cancer According to Tumor HPV Status or p16-Expression Status

A. Overall Survival According to Tumor HPV Status

- HPV-positive
- HPV-negative

B. Progression-free Survival According to Tumor HPV Status

- HPV-positive
- HPV-negative

C. Overall Survival According to p16 Expression

- p16-positive
- p16-negative

D. Progression-free Survival According to p16 Expression

- p16-positive
- p16-negative

Patients with Stage III (excluding T1-2N1) or IV SCCHN (stratified by stage, site, hemoglobin)

Randomization

Cisplatin, RT

Tirapazamine, cisplatin, RT

No significant difference in overall survival
Radiotherapy deviations had a major adverse impact on treatment outcome
Overall Survival – p16

HR = 0.35; P = 0.004
2-year OS: .92% & 74%

P16+ (107)
P16- (79)
Time to Locoregional Failure by Treatment Arm

HPV + &/or p16 +

HPV - / p16-

HR = 0.34; P = 0.13
2-year rates: 90% & 77%

HR = 0.52; P = 0.69
2-year rates: 96% & 93%
RTOG 0522: Study Objective & Design

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

Stratify:
- Lx vs Non-Lx
- N0 vs N1-2b vs N2c-3
- Zubrod PS
- 3-D vs IMRT
- PET (yes vs no)

Excluded T1N+, T2N1

1. AFX-CB: 72 Gy/42 F/6 W +
   Cisplatin: 100 mg/m², q3W x 2

2. AFX-CB: 72 Gy/42 F/6 W +
   Cisplatin: 100 mg/m², q3w x 2
   Cetuximab: 400 mg/m² x 1,
   then 250 mg/m²/w
RTOG 0522: Statistics

- Primary endpoint: PFS
- Targeted sample size: 940
- Hazard ratio: 0.75
- Statistical power: 84% (1-sided $\alpha = 0.025$)
- Interim analyses (108, 217, 325 events)
- Planned subset analyses: treatment effect by p16 subgroups
RTOG 0522: Study Population

Accrual: 940 patients in <3.5 years (11/’05 - 03/’09)

No Follow-Up: 2

Found Ineligible on Review: 43

Analyzeable: 895 (95%)

Median FU (pts alive): 2.4 years (0.01 - 4.8)

RT+Cisplatin: 448

RT+Cisplatin+Cet: 447
# RTOG 0522: Patient & Tumor Features

<table>
<thead>
<tr>
<th>RT + Cisplatin</th>
<th>Cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (448)</td>
</tr>
<tr>
<td>Age</td>
<td>57 (31-79)</td>
</tr>
<tr>
<td>Gender - Male</td>
<td>87%</td>
</tr>
<tr>
<td>Zubrod: 0 - 1</td>
<td>65% - 35%</td>
</tr>
<tr>
<td>Primary site</td>
<td></td>
</tr>
<tr>
<td>✓ Oropharynx</td>
<td>70%</td>
</tr>
<tr>
<td>✓ Larynx</td>
<td>23%</td>
</tr>
<tr>
<td>T3-4</td>
<td>62%</td>
</tr>
<tr>
<td>N+</td>
<td>90%</td>
</tr>
<tr>
<td>AJCC stage IV</td>
<td>87%</td>
</tr>
<tr>
<td>RT + Cisplatin</td>
<td>Cetuximab</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>RT ≥ 66 Gy</td>
<td>97%</td>
</tr>
<tr>
<td>RT – major deviations (CTVs, etc)</td>
<td>7.1%</td>
</tr>
<tr>
<td>RT – not evaluable (CTVs, etc)</td>
<td>3.6%</td>
</tr>
<tr>
<td>Cisplatin: 2 cycles</td>
<td>94%</td>
</tr>
<tr>
<td>Cetuximab: &lt;6 weeks</td>
<td>N/A</td>
</tr>
<tr>
<td>Not per protocol, &lt;80% dose</td>
<td>6%</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>1%</td>
</tr>
</tbody>
</table>
RTOG 0522
Progression-Free Survival & Overall Survival

**Primary Endpoint**

Hazard Ratio (95% CI)  
1.05 (0.84, 1.29)  
\( P = 0.66 \) (log-rank, 1-sided)

2-Year Rate (95% CI)  
- Cisplatin: 64.3% (59.7, 68.8)  
- Cisplatin+Cet: 63.4% (58.7, 68.0)

**Overall Survival (%)**

Hazard Ratio (95% CI)  
0.87 (0.66, 1.15)  
\( P = 0.17 \) (log-rank, 1-sided)

2-Year Rate (95% CI)  
- Cisplatin: 79.7% (75.9, 83.6)  
- Cisplatin+Cet: 82.6% (78.9, 86.3)

# Patients at Risk

<table>
<thead>
<tr>
<th>Years after Randomization</th>
<th>Cisplatin</th>
<th>Cisplatin+Cet</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 years</td>
<td>448</td>
<td>447</td>
</tr>
<tr>
<td>1 year</td>
<td>316</td>
<td>302</td>
</tr>
<tr>
<td>2 years</td>
<td>217</td>
<td>197</td>
</tr>
<tr>
<td>3 years</td>
<td>78</td>
<td>80</td>
</tr>
</tbody>
</table>

# Patients at Risk

<table>
<thead>
<tr>
<th>Years after Randomization</th>
<th>Cisplatin</th>
<th>Cisplatin+Cet</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 years</td>
<td>448</td>
<td>447</td>
</tr>
<tr>
<td>1 year</td>
<td>385</td>
<td>378</td>
</tr>
<tr>
<td>2 years</td>
<td>266</td>
<td>251</td>
</tr>
<tr>
<td>3 years</td>
<td>96</td>
<td>94</td>
</tr>
</tbody>
</table>
# RTOG 0522: Acute Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Cetuximab</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (448)</td>
<td>Yes (447)</td>
<td></td>
</tr>
<tr>
<td><strong>RT + Cisplatin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead of any cause ((P = 0.81))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 30 days after Rx ended</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 (2%)</td>
<td>9 (2%)</td>
<td></td>
</tr>
<tr>
<td>Worst Overall ((P = 0.92))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>43 (10%)</td>
<td>39 (9%)</td>
<td></td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>388 (87%)</td>
<td>387 (86%)</td>
<td></td>
</tr>
<tr>
<td>Grade 5</td>
<td>1 (&lt;1%)</td>
<td>5 (1%)</td>
<td></td>
</tr>
<tr>
<td>Worst Non-Hematologic ((P = 0.41))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>59 (13%)</td>
<td>48 (11%)</td>
<td></td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>371 (83%)</td>
<td>376 (84%)</td>
<td></td>
</tr>
<tr>
<td>Grade 5</td>
<td>1 (&lt;1%)</td>
<td>5 (1%)</td>
<td></td>
</tr>
</tbody>
</table>
## RTOG 0522: Acute Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (448)</td>
</tr>
<tr>
<td></td>
<td>Yes (447)</td>
</tr>
</tbody>
</table>

### Mucositis ($P = 0.004$)

<table>
<thead>
<tr>
<th>Grade</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>126 (28%)</td>
<td>85 (19%)</td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>174 (39%)</td>
<td>172 (38%)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>148 (33%)</td>
<td>190 (43%)</td>
</tr>
</tbody>
</table>

### Skin Reactions - In-field ($P < 0.001$)

<table>
<thead>
<tr>
<th>Grade</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>98 (22%)</td>
<td>104 (23%)</td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>285 (64%)</td>
<td>231 (52%)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>65 (15%)</td>
<td>112 (25%)</td>
</tr>
</tbody>
</table>

### Skin Reactions - Out-field ($P < 0.001$)

<table>
<thead>
<tr>
<th>Grade</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>385 (86%)</td>
<td>87 (19%)</td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>60 (13%)</td>
<td>273 (61%)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>3 (1%)</td>
<td>87 (19%)</td>
</tr>
<tr>
<td>RT + Cisplatin</td>
<td>Cetuximab</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>-----------</td>
<td>-------------</td>
</tr>
<tr>
<td></td>
<td>No (448)</td>
<td>Yes (447)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P = 0.62$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>78 (18%)</td>
<td>65</td>
</tr>
<tr>
<td>(16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>202 (47%)</td>
<td>199</td>
</tr>
<tr>
<td>(48%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>152 (35%)</td>
<td>154</td>
</tr>
<tr>
<td>(37%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worst Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P = 0.06$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>197 (46%)</td>
<td>160 (38%)</td>
</tr>
<tr>
<td>(58%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 5</td>
<td>2 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>
### RTOG 0522

**Outcome by p16 Status and Treatment Regimen**

(HR <1 indicates benefit for the cetuximab arm)

<table>
<thead>
<tr>
<th>Oropharynx</th>
<th>P-F Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ p16-pos (N=235)</td>
<td><img src="#" alt="Diamond" /></td>
<td><img src="#" alt="Square" /></td>
</tr>
<tr>
<td>✓ p16-neg (N=86)</td>
<td><img src="#" alt="Square" /></td>
<td><img src="#" alt="Square" /></td>
</tr>
<tr>
<td>✓ No specimens (N=307)</td>
<td><img src="#" alt="Square" /></td>
<td><img src="#" alt="Square" /></td>
</tr>
</tbody>
</table>

| Non-oropharynx (N=267)    | ![Square](#)  | ![Square](#)     |

| All patients (N=895)      | ![Square](#)  | ![Square](#)     |

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**Hazard Ratio with 95% Confidence Interval**

**Head and Neck Cancer**

7th Annual Multidisciplinary Symposium

November 19th, 2011 • Hyatt at the Bellevue • Philadelphia, PA
Survival R0129 Patients with Oropharyngeal Cancer According to Tumor HPV Status or p16-Expression Status

Underappreciation of XRT Morbidity

**E1308**
Induction followed by IMRT/Cetuximab

**ELIGIBILITY**
- Stage III/IVa,b
- p16+
- Oropharynx

**INDUCTION**
(3 cycles)
- Paclitaxel
- CDDP
- Cetuximab

**CONCURRENT**
- IMRT 54Gy
- Cetuximab wkly

**CONCURRENT**
- IMRT 69.3Gy
- Cetuximab wkly

Goal is to maintain outstanding PFS and minimize late toxicity

Completed accrual October, 2011

Head and Neck Cancer
7th Annual Multidisciplinary Symposium
November 19th, 2011 • Hyatt at the Bellevue • Philadelphia, PA
Cetuximab-RT vs ChemoRT

**Eligibility**

- **Oropharynx**
  - P16 pos
  - T1-2, N2a-3 or T3-4 any N

**Stratify**

- **T-stage**
  - T 1,2
  - T 3,4

- **N-stage**
  - N0-2A
  - N2B-C

- **Smoking**
  - <10 PY
  - >10 PY

- **Zubrod**
  - 1
  - 2

**Randomize**

- AFX 70 Gy for 6 wks + cisplatin x 2
- AFX 70 Gy for 6 wks + cetuximab for 8 wks

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**Notes**

- N=700
- 3.8 yrs to enroll
- ~8 yr to analysis

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**Anticipated Launch:** March 2011

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**Head and Neck Cancer**

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**RTOG**

Radiation Therapy Oncology Group

www.rtog.org
HPV Negative Cancer

- High mutational burden
- p53 often mutated, p16 LOH common
- EGFR overexpressed
- Treatment resistant
  - Improvements in outcome attributed to induction, accelerated radiation, other intensifications may have resulted from unrecognized HPV + favorable risk patients
CU DC-101 with CDDP and Radiation in HPV-Negative Head and Neck Cancer

EGFR/HER2/HDAC inhibitor
Superior potency to erlotinib in multiple cell lines and xenografts, including erlotinib resistant cell lines.

Currently completed phase I dose escalation trial in advanced and refractory solid tumors has shown that CU DC-101 is well tolerated with good pharmacokinetics. Evidence of clinical antitumor activity observed in this heavily pretreated patient population, incl 1 pt with HNC
**CUDC-101 Structure Design:** integrating a hydroxamic acid HDAC-inhibiting moiety into quinazoline RTK inhibition pharmacophore

<table>
<thead>
<tr>
<th>HDAC Inhibitors</th>
<th>EGF/Her2 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAHA</td>
<td>erlotinib</td>
</tr>
<tr>
<td>MW 264.3</td>
<td>MW 393.5</td>
</tr>
<tr>
<td>Belinostat</td>
<td>lapatinib</td>
</tr>
<tr>
<td>MW 318.35</td>
<td>MW 581.1</td>
</tr>
<tr>
<td>JNJ-16241199</td>
<td>gefitinib</td>
</tr>
<tr>
<td>MW 413.45</td>
<td>MW 446.9</td>
</tr>
</tbody>
</table>

**HDAC/ EGF/Her2 Inhibitors**

- CUDC-101
  - MW 434.5
CUDDC-101 Disrupts Signaling Network to Improve the Treatment of Heterogeneous and Drug-Resistance Tumors

Receptors

Signaling Molecules

Transcription Factors

EGFR       HER2       HER3       MET

p-Akt

p53

ER

HIF-1α

Control  SAHA  CUDC-101  erlotinib  erlotinib  SAHA  CUDC-101

Ac-p53

p53

HIF-1α

Tubulin

Akt

MAPK Signaling

Akt Signaling

EGFR/Her2

HER3

MET

Tubulin

Ctrl  CUDC-101  erlotinib  SAHA

Ctrl  CUDC-101  erlotinib

Ctrl  CUDC-101  erlotinib

Ctrl  CUDC-101  erlotinib

Ctrl  CUDC-101  erlotinib

Ctrl  CUDC-101  erlotinib

Ctrl  CUDC-101  erlotinib

Ctrl  CUDC-101  erlotinib
• **Cisplatin** 100 mg/m² IV on d 2, 22 and 44 of 7 week radiation course using conventional fractionation

• **CUDC-101 Therapy**

• Initial dose of CUDC-101 225 mg/m².

• This dose is 80% of the MTD established in the previous Phase I mono-therapy study.
  - Dose level +1: 275 mg/m²
  - Dose level -1: 175 mg/m².
  - Dose level -2: 150 mg/m²

• **CUDC-101** given by IV infusion over 1 hour 3 times per week (M, W, F) for weeks 1-3 and 5-7. (i.e. Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 29, 31, 33, 36, 38, 40, 43, 45, 47). No CUDC-101 will be administered during week 4.
Is There An Intermediate Risk Cohort?

Confirms single institution data U of M

Some reservations:
- RPA retrospective analysis
- Based on small numbers
- Tobacco histories second hand
- Utilized HPV not p16
- OS endpoint susceptible to confounding by comorbidities in smokers

How Does Minimally Invasive Surgery Contribute

- HPV associated cancers may be smaller, more amenable to modern transoral approaches
- Relative sparing of radiation dose may be studied – CTPM
- Comparison of induction chemo vs. transoral surgery as RT sparing manoeuvres not an immediate study design
Conclusions

• Radiation to 66-70Gy with full dose cisplatin remains the standard of care
• Contribution of induction chemotherapy awaits report of DeCIDE trial
• Contribution of cetuximab to cisplatin/RT not supported by R0522, although toxicity is increased
  – Results quite preliminary
• HPV associated disease may be curable with less morbid therapy but this HAS NOT been proven
• Non-HPV associated disease requires novel treatment approaches