Head and Neck Cancer:

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Predictive Biomarkers: HPV

- Abstract 6003: Survival Outcomes By HPV Status In Oropharyngeal Cancer In RTOG 0129, Gillison, et al

- Abstract 6004: Prognostic Significance Of HPV And P16 Status In Patients With Oropharyngeal Cancer Treated On A Large International Phase III Trial, Rischin, et al

- Abstract 6001: The Implication of Tobacco Usage in the Development of Distant Metastases & Tumor Recurrence in Patients with HPV (+) Squamous Cell Cancers of the Oropharynx : F Worden et al
Predictive Biomarkers: Other

- **Abstract 6000**: Mass spectrometry profile as a predictor of overall survival benefit after treatment with epidermal growth factor receptor inhibitors in head and neck squamous cell carcinoma

- **Abstract 6005**: Biomarker Potential Of *EGFR* Gene Copy Number In The Phase III EXTREME Study: Platinum-based CT ± Cetuximab In R/M SCCHN, Licitra, et al
Abstract 6003

Survival Outcomes By HPV Status In Oropharyngeal Cancer In RTOG 0129

Gillison, et al
Results Of Laboratory Analysis

- 433 (60%) Of 721 Had Oropharynx Primary
- 323 (75%) Of 433 Had HPV Determination
- 206 (64%) Of 323 Were HPV-positive
- 198 (96%) Of 206 Were HPV16-positive

<table>
<thead>
<tr>
<th></th>
<th>P16-positive</th>
<th>P16-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-positive</td>
<td>192 (96%)</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>HPV-negative</td>
<td>22 (19%)</td>
<td>94 (81%)</td>
</tr>
</tbody>
</table>

Kappa = 0.80: 95%CI 0.73-0.87

Gillison, et al
## Two-year Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>HPV-Positive (%)</th>
<th>HPV-Negative (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td>87.9</td>
<td>65.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Progression-free Survival</strong></td>
<td><strong>71.8</strong></td>
<td>50.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Local-regional Failure</td>
<td>13.6</td>
<td>24.8</td>
<td>0.004</td>
</tr>
<tr>
<td>Distant Metastases</td>
<td>9.7</td>
<td>12.9</td>
<td>0.26</td>
</tr>
<tr>
<td>Second Primary Tumor</td>
<td>3.9</td>
<td>11.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Aerodigestive SPT</td>
<td>2.9</td>
<td>7.7</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Gillison, et al.
Overall Survival by HPV Status

Patients at Risk
HPV Pos. 206
HPV Neg. 117

Years after Randomization
0 1 2 3 4 5

HPV Positive
HPV Negative

log-rank p<0.001

Patients at Risk
HPV Pos. 206
HPV Neg. 117

Years after Randomization
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Years after Randomization
0 1 2 3 4 5

HPV Positive
HPV Negative

log-rank p<0.001

5-year Difference 29%; 95% CI: 12-45

Gillison, et al
<table>
<thead>
<tr>
<th>Variable</th>
<th>HPV-Positive</th>
<th>HPV-Negative</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment, SFX (%)</td>
<td>51.5</td>
<td>50.4</td>
<td>0.86</td>
</tr>
<tr>
<td>Age, Years (Median)</td>
<td>53.5</td>
<td>57.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Race, White (%)</td>
<td>92.2</td>
<td>75.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Zubrod PS, 0 (%)</td>
<td>68.4</td>
<td>56.4</td>
<td>0.03</td>
</tr>
<tr>
<td>AJCC Stage, IV (%)</td>
<td>87.9</td>
<td>83.8</td>
<td>0.30</td>
</tr>
<tr>
<td>T Stage, 2-3 (%)</td>
<td>75.2</td>
<td>60.7</td>
<td>0.008</td>
</tr>
<tr>
<td>N Stage, N0-2a (%)</td>
<td>30.1</td>
<td>38.5</td>
<td>0.14</td>
</tr>
<tr>
<td>Pack-years, &lt; 20 (%)</td>
<td>51.0</td>
<td>22.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Gillison, et al
## Tumor HPV, Smoking Status, and OS

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-positive, &lt;20 pack-years</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>HPV-positive, ≥ 20 pack-years</td>
<td>1.91</td>
<td>1.20 - 3.05</td>
</tr>
<tr>
<td>HPV-negative, &lt; 20 pack-years</td>
<td>2.25</td>
<td>1.44 - 3.50</td>
</tr>
<tr>
<td>HPV-negative, ≥ 20 pack-years</td>
<td>4.30</td>
<td>2.40 - 7.71</td>
</tr>
</tbody>
</table>

Adjusted for age, race, T stage, N stage, and treatment assignment

Gillison, et al
Abstract 6004

Prognostic Significance Of HPV And P16 Status In Patients With Oropharyngeal Cancer Treated On A Large International Phase III Trial

Rischin, et al
# Results of Laboratory Analysis

## Head Start Trial

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Entered Into the Study</td>
<td>853</td>
</tr>
<tr>
<td>Total Oropharynx</td>
<td>465</td>
</tr>
<tr>
<td>Total Slides Available</td>
<td>228</td>
</tr>
<tr>
<td>Total Minimal Compliance (60-70 cGy)</td>
<td>208</td>
</tr>
<tr>
<td>HPV Tested</td>
<td>195</td>
</tr>
<tr>
<td><em>Positive</em></td>
<td>54 (28%)</td>
</tr>
<tr>
<td>P16 Tested</td>
<td>186</td>
</tr>
<tr>
<td><em>Positive</em></td>
<td>107 (58%)</td>
</tr>
<tr>
<td>Patient Characteristics</td>
<td>HPV -</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Male</td>
<td>83%</td>
</tr>
<tr>
<td>Median Age</td>
<td>56</td>
</tr>
<tr>
<td>T Stage 3-4</td>
<td>75%</td>
</tr>
<tr>
<td>N Stage 2-3</td>
<td>73%</td>
</tr>
<tr>
<td>ECOG PS 0</td>
<td>65%</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>37%</td>
</tr>
</tbody>
</table>

* P < 0.05

Rischin, et al
Overall Survival – HPV+ / HPV-

HR = 0.27; P = 0.007
2-year OS: 94% & 77%

Rischin, et al
Site of First Failure

Percentage of patients

- HPV+ &/or p16+
- HPV- & p16-

Rischin, et al
Abstract 6001

The Implication of Tobacco Usage in the Development of Distant Metastases & Tumor Recurrence in Patients with HPV (+) Squamous Cell Cancers of the Oropharynx

F Worden et al
Univ of Michigan Protocol 9921
Overall Survival by HPV-16 Status

4 yr survival = 70.4%, 95%CI = (57.5%, 80.0%)

p=0.006

Worden et al. JCO 2008
Questions Outstanding

• Why do some patients with HPV (+) tumors ultimately die from disseminated disease?

• Do smokers with HPV (+) tumors have the same favorable prognosis as non-smokers?

• Can treatment for HPV (+) tumors be tailored based on smoking status?
Objectives

• To evaluate the association of HPV status with long-term outcomes in oropharynx cancer patients.

• To evaluate the effect of tobacco use on long-term outcomes in HPV positive (+) oropharynx cancer patients.
Methods

- **Retrospective Review:** 124 patients with stage III/IV SCC of the oropharynx, treated on 2 sequential phase II, chemoradiotherapy protocols.

- Adequate tumor DNA for HPV analysis.

- All were candidates for surgical resection.
Tobacco Usage

• History of tobacco use: cigarettes, cigars, pipes, and chewing tobacco

• Determined via two methods:
  1. Chart review
  2. Self-reporting at the time of study enrollment

• Discrepancies: cross-referenced with the treating physicians
Definitions of Tobacco Usage

- **Never**: never used chewing tobacco, cigars, or pipes, with the equivalent of < 100 cigarettes in a lifetime.

- **Current**: present, including those who quit < 1 year prior to diagnosis.

- **Former**: quit > 1 year prior to diagnosis.
### Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Study Group</strong></td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>103</td>
<td>83%</td>
</tr>
<tr>
<td>Female</td>
<td>21</td>
<td>17%</td>
</tr>
<tr>
<td><strong>Median Age</strong></td>
<td>57 years</td>
<td></td>
</tr>
<tr>
<td>HPV (+)</td>
<td>102</td>
<td>82%</td>
</tr>
<tr>
<td>HPV (-)</td>
<td>22</td>
<td>18%</td>
</tr>
<tr>
<td>HPV (+) Never Tobacco</td>
<td>33</td>
<td>27%</td>
</tr>
<tr>
<td>HPV (+) Any Tobacco</td>
<td>69</td>
<td>56%</td>
</tr>
<tr>
<td>HPV (-) Never Tobacco</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>HPV (-) Any Tobacco</td>
<td>22</td>
<td>18%</td>
</tr>
<tr>
<td><strong>Base of Tongue</strong></td>
<td>62</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Tonsil</strong></td>
<td>57</td>
<td>46%</td>
</tr>
<tr>
<td><strong>Other Oropharynx</strong></td>
<td>5</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Stage III</strong></td>
<td>17</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Stage IVA</strong></td>
<td>92</td>
<td>74%</td>
</tr>
<tr>
<td><strong>Stage IVB</strong></td>
<td>15</td>
<td>12%</td>
</tr>
</tbody>
</table>
# Patient Characteristics

<table>
<thead>
<tr>
<th>Tobacco Use</th>
<th>Total</th>
<th>HPV+ (n=102)</th>
<th>HPV- (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>33</td>
<td>33 (32%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Former</td>
<td>52</td>
<td>46 (45%)</td>
<td>6 (28%)</td>
</tr>
<tr>
<td>Current</td>
<td>39</td>
<td>23 (23%)</td>
<td>16 (72%)</td>
</tr>
</tbody>
</table>
Results

• Objective (1): HPV Incidence and its effect on recurrence, OS, and DSS

• Objective (2): The effect of tobacco on long-term outcomes among HPV + patients
### HPV Incidence by Cohort

<table>
<thead>
<tr>
<th></th>
<th>UMCC 9921</th>
<th>UMCC 0221</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV (-)</td>
<td>14 (34%)</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>HPV (+)</td>
<td>27 (66%)</td>
<td>75 (90%)</td>
</tr>
</tbody>
</table>
## Patterns of Recurrent Disease by HPV Status and Use of Tobacco

<table>
<thead>
<tr>
<th></th>
<th>HPV+</th>
<th>HPV-</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Never-Tobacco User</strong></td>
<td>2/33 (6%)</td>
<td>0/0</td>
</tr>
<tr>
<td>Loco-Regional</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Distant Metastases</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Second Primary</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Current</strong></td>
<td>8/23 (35%)</td>
<td>8/16 (50%)</td>
</tr>
<tr>
<td>Loco-Regional</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Distant Metastases</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Second Primary</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Former</strong></td>
<td>9/46 (20%)</td>
<td>3/6 (50%)</td>
</tr>
<tr>
<td>Loco-Regional</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Distant Metastases</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Second Primary</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
### Risk of Recurrence*  
**HPV (+) Patients**

<table>
<thead>
<tr>
<th>Tobacco Status</th>
<th>Hazard Ratio</th>
<th>(95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current vs Never</td>
<td>5.2</td>
<td>(1.1-24.4)</td>
<td>0.038</td>
</tr>
<tr>
<td>Former vs Never</td>
<td>2.9</td>
<td>(0.6-13.6)</td>
<td>0.18</td>
</tr>
<tr>
<td>Current vs Former</td>
<td>1.8</td>
<td>(0.7-4.8)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

* p= 0.063 for overall effect of tobacco using Cox proportional hazards model adjusting for cohort effect.
Time to Recurrence in HPV (+) Patients by Tobacco Usage

Tobacco effect from Cox Model $p=0.063$ (adjusting for cohort effect)
### Disease Specific Survival*  
**HPV (+) Patients**

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<tr>
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<th>(95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current vs Never</td>
<td>7.2</td>
<td>(0.88-58.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>Former vs Never</td>
<td>3.6</td>
<td>(0.43-30.1)</td>
<td>0.24</td>
</tr>
<tr>
<td>Current vs Former</td>
<td>1.99</td>
<td>(0.66-6.03)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

* p= 0.064 for overall effect of tobacco using Cox proportional hazards model adjusting for cohort effect.
Disease Specific Survival by Cohort and Tobacco Usage

Tobacco effect from Cox Model $p=0.064$
(adjusting for cohort effect)
Conclusions

• HPV (+) tumors have more favorable OS and DSS compared to HPV (-) tumors.

• HPV (+) tumors have lower risk of disease recurrence.

• Patients who are HPV (+) and are current tobacco users have a higher risk of disease recurrence compared to HPV (+) never-tobacco users.
HPV and Prognosis

Gillison et al

- Tumor HPV Status Is A Strong And Independent Predictor Of OS And PFS.
- Rates For Local-regional and Not Distant Recurrence Were Lower in HPV+ Patients
- P16 Is Highly Correlated With Tumor HPV Status And Is Valid Surrogate.
- Tobacco Use Appears To Modify The Biological Behavior Of HPV+ Tumors
- Tumor HPV Status Or P16 Must Be A Stratification Factor In Clinical Trials That Include Oropharynx Patients.

Rischin et al

- HPV Positive Oropharyngeal Cancer is Associated With Improved Prognosis
- p16 Identifies A Larger Group With An Improved Prognosis
- Future Head And Neck Cancer Trials Require Stratification By HPV Or P16 Status
- Information About HPV Status And Radiation Quality Important For Interpretation Of Trials Of Chemoradiation In Head And Neck Cancer
HPV and Prognosis: Conclusions

• HPV Related HNC Is A Unique Disease
  – Better Prognosis Based On LRC
  – Different Biology

• The Demographic Profile Of HPV+ HNC Supports A Better Outcome
  – PS, Age, Smoking, Ethnicity
  – Reduced Second Primary, Death From “Non-Cancer Causes”
  – Better Compliance

• Survival Statistics Are Early
  – Distant Metastases Are Likely to Occur Late
  – PFS More Directly Predicts Cancer Mortality In Oropharynx, This is a Young Population, Hence Longer Follow Up is Needed to Better Understand Outcomes
Abstract 6005

Biomarker Potential Of EGFR Gene Copy Number In The Phase III EXTREME Study: Platinum-based CT ± Cetuximab In R/M SCCHN

Licitra, et al
EXTREME study design

Randomized, phase III, multicenter study (n=442)

CT alone (n=220)

Cetuximab + CT (n=222) — Maintenance

Cetuximab until progression*
Overview of EGFR Signals

- Tumors from 312 of the 442 patients (71%) in the ITT population were evaluable by FISH.
- Treatment arms were similar in terms of:
  - EGFR signals
  - Clinical outcomes

<table>
<thead>
<tr>
<th>Cell count/patient, median (range)</th>
<th>Cetuximab + CT (n=158)</th>
<th>CT alone (n=154)</th>
<th>All patients (n=312)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEP7</td>
<td>2.3 (1.1–6.2)</td>
<td>2.4 (1.2–5.8)</td>
<td>2.3 (1.1–6.2)</td>
</tr>
<tr>
<td>EGFR</td>
<td>2.6 (1.1–26.8)</td>
<td>2.8 (1.0–43.2)</td>
<td>2.7 (1.0–43.2)</td>
</tr>
<tr>
<td>EGFR:CEP7</td>
<td>1.0 (0.6–10.7)</td>
<td>1.1 (0.5–20.8)</td>
<td>1.1 (0.5–20.8)</td>
</tr>
</tbody>
</table>

CEP7, centromere-specific probe for chromosome 7; CT, chemotherapy; FISH, fluorescence in situ hybridization.
No Association Between Overall Survival And FISH Score

- In either treatment arm
- For any model

CT, chemotherapy; FISH, fluorescence in situ hybridization; OS, overall survival
Conclusions

Cetuximab Benefit in HNC

- Not Associated with Increased EGFr Copy Number
- Not associated with Known EGFr Mutations
- Not Associated with Mutations in Known Signaling Pathways
- Is Associated with Rash
Abstract 6000

Mass spectrometry profile as a predictor of overall survival benefit after treatment with epidermal growth factor receptor inhibitors in head and neck squamous cell carcinoma

Chung et al
Introduction

• Epidermal growth factor receptor (EGFR) pathway is deregulated in head and neck squamous cell carcinoma (HNSCC)
  • Overexpression of EGFR by immuno-staining
  • Increased *EGFR* gene copy number by fluorescence in situ hybridization
• EGFR inhibitors have shown to provide clinical benefits in HNSCC patients although response rates to monotherapy are low (4-13%)

=> **It is important to identify biomarkers of clinical benefit**
Current Biomarkers for EGFR Inhibitor Therapy

- EGFR tyrosine kinase domain mutations associated with response in lung cancer is extremely rare in HNSCC (Chung, et al. JCO 2006)
- KRAS mutations associated with resistance in colon cancer are present in only 3.5% of HNSCC (Bissada, et al. ASCO 2008)
- Increased EGFR gene copy number does not predict response to cetuximab in HNSCC (Licitra, et al. ASCO 2009)
- Currently there is no validated biomarker that predicts clinical benefits of EGFR inhibitors in HNSCC
Background

• In a previous study, a mass spectrometry (MS) profile from serum and plasma samples from non-small cell lung cancer (NSCLC) patients can predict the overall survival after the treatments with EGFR TK inhibitors, gefitinib or erlotinib (Taguchi, et al. JNCI, 2007)

• The profile contains 8 distinguishing MS peaks

• The assay is currently commercialized as VeriStrat®
Subset Analysis of NSCLC Patients with Squamous Cell Histology treated with EGFR-TKIs

N=37 (20 Good, 17 Poor)

Median survival
65.3 weeks (Good)
14.4 weeks (Poor)

p<0.0001, HR=0.17
HNSCC Study

- **Hypothesis:** The MS profile is reflective of EGFR dependency of the tumor regardless of the histology.

- Therefore, the profile may be predictive of overall survival in HNSCC patients with the tumors dependent on EGFR pathway, treated with various types of EGFR inhibitors.
HNSCC Sample Description

- **EGFR inhibitor treated cohorts**
  - N= 55, Phase II recurrent and/or metastatic (R/M) patients, Gefitinib 250 mg once daily
  - N= 32, Phase II R/M patients, Erlotinib 150 mg once daily and Bevacizumab 15 mg/kg every three weeks
  - N= 21, R/M patients, Cetuximab 400 mg/m² loading dose and 250 mg/m² once a week
HNSCC Sample Description

- **Control cohorts**
  - N= 78, HNSCC patients at the time of diagnosis treated with surgery as a primary therapy
  - N= 34, Two phase II clinical trials with identical eligibility criteria, R/M HNSCC treated with docetaxel/bortezomib or docetaxel/irinotecan combinations
Classification based on the MALDI MS Algorithm

<table>
<thead>
<tr>
<th>Cohorts</th>
<th>Gefitinib (n=55)</th>
<th>Erlotinib/Bev (n=32)</th>
<th>Cetux (n=21)</th>
<th>Control #1 surgical (n=78)</th>
<th>Control #2 no EGFRI (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good (%)</td>
<td>31 (56)</td>
<td>24 (75)</td>
<td>16 (76)</td>
<td>77 (99)</td>
<td>22 (65)</td>
</tr>
<tr>
<td>Poor (%)</td>
<td>23 (42)</td>
<td>6 (19)</td>
<td>5 (24)</td>
<td>1 (1)</td>
<td>12 (35)</td>
</tr>
<tr>
<td>Undefined (%)</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Failed MS (%)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
Overall Survival based on the MS Profile

**Gefitinib**
- P=0.007
- HR=0.41, 95% CI 0.22-0.79
- Median time to death:
  - Good 36.7 weeks
  - Poor 18.0 weeks

**Erlotinib/bevacizumab**
- P=0.02
- HR=0.20, 95% CI 0.05-0.78
- Median time to death:
  - Good 39.5 weeks
  - Poor 29.1 weeks
Overall Survival based on the MS Profile

Cetuximab

P = 0.06
HR = 0.26, 95% CI 0.06-1.06
Median time to death:
Good 38.3 weeks
Poor 11.9 weeks

Chemotherapy

P = 0.76
HR = 0.88, 95% CI 0.4-1.94
Median time to death:
Good 39.4 weeks
Poor 15.5 weeks
Conclusions

• This study suggests that;
  – The same predictive algorithm for MALDI-MS (VeriStrat\textsuperscript{R}) generated from EGFR TKI-treated patients with NSCLC is also predictive of survival outcome in HNSCC patients
  – The profile is predictive in both small molecule EGFR TKI- and cetuximab-treated patients

• Application of the proteomic profile may allow rational selection of patients most likely to benefit from an EGFRI Monotherapy and EGFRI-containing combination therapy
Chemotherapy in SCCHN

Abstract 6009

Final Results Of A Phase III Trial Comparing Induction Chemotherapy PF or TPF Followed By Chemoradiotherapy vs CRT Alone for Unresectable Locally Advanced Head And Neck Cancer

Hitt et al
Curative Treatment of SCCHN:

- TPF is the Standard of Care for Induction Chemotherapy
- Which is the Better Therapy for Survival?
  - Sequential Therapy or Chemoradiotherapy
- Which is the Better Therapy for Organ Preservation?
  - Sequential Therapy, Induction Therapy (Followed by RT), or Chemoradiotherapy

Posner, 2007; Vermorken 2007; Pointreau, 2009
Study Design

N=439

R

PF 3 cycles q3w
CRT

TPF 3 cycles q3w
CRT

Neck dissection
Surgery
Statistical hypothesis

• Planned sample size: 438 patients
  – To show an increase of 50% in median TTF* for ICT/CRT versus CRT, 8 to 12 months, HR=0.67, \( \alpha=0.05 \); power=80%

• Analysis Populations:
  – Efficacy ITT: All randomized patients
  – Efficacy Evaluable: Patients with at least 1 cycle of CRT and/or ICT and all early progressions and deaths due to tumor
  – Safety: All patients with at least 1 dose of study treatment
## Tumor characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CRT (N=128)</th>
<th>PF plus CRT (N=156)</th>
<th>TPF plus CRT (N=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary tumor site, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>42</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>18</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Larynx</td>
<td>20</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>20</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td><strong>TN stage (primary), %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4 N0</td>
<td>15</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>T4 N1</td>
<td>20</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>T4 N2</td>
<td>34</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td>T4 N3</td>
<td>5</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total T4 (N0/1/2/3), %</strong></td>
<td>74</td>
<td>80</td>
<td>76</td>
</tr>
</tbody>
</table>
## Summary of efficacy

<table>
<thead>
<tr>
<th></th>
<th>CRT (N=119)</th>
<th>PF plus CRT (N=123)</th>
<th>TPF plus CRT (N=111)</th>
<th>Total ICT (TPF + PF) (N=234)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median HR (95% CI) vs CRT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TTF</strong></td>
<td>5.0</td>
<td>12.3</td>
<td>13.4</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td>0.60 (0.44–0.80)</td>
<td>0.55 (0.41–0.75)</td>
<td>0.57 (0.45–0.74)</td>
<td></td>
</tr>
<tr>
<td><strong>TTP</strong></td>
<td>13.1</td>
<td>18.5</td>
<td>20.4</td>
<td>18.5</td>
</tr>
<tr>
<td></td>
<td>0.83 (0.61–1.13)</td>
<td>0.74 (0.53–1.02)</td>
<td>0.79 (0.60–1.03)</td>
<td></td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>27.1</td>
<td>33.6</td>
<td>37.2</td>
<td>37.1</td>
</tr>
<tr>
<td></td>
<td>0.87 (0.62–1.24)</td>
<td>0.82 (0.57–1.18)</td>
<td>0.85 (0.63–1.15)</td>
<td></td>
</tr>
</tbody>
</table>

86 Patients Missing in the Analysis
Conclusions

• Further Analysis and Review of the Data Are Needed and Conclusions are Limited Due to:
  • End Point Selection (TTF)
  • Missing Patients in All Arms (ITT Analysis)

• The Question: Which is the Better Treatment for Survival in LAHNC - Sequential Therapy (ICT + CRT) or Bolus Cisplatin-CRT – Remains Open
Toxicity/Supportive Care

Abstract 6007

Randomized Study of Darbepoetin Alpha as a Modifier of radiotherapy in Patients with HNC: Final Outcome of the DAHANCA 10 Trial

Overgaard et al
The study aimed to evaluate if correction of low hemoglobin levels by means of the erythropoietin stimulating agent: Darbepoetin alpha (Aranesp) during radiotherapy (RT) improves outcome in patients with HNSCC.
Design and Treatment

- Pts with HNSCC, eligible for primary RT alone.
- Hgb values below 14.0 g/dl
- Randomized to receive Aranesp together with accelerated fractionated RT.
- Pts were stratified according to gender, T and N staging, tumor site, and institution.
- Aranesp was given subcutaneously in a dose of 150 micrograms weekly during RT, or stopped earlier if the Hgb exceeded 15.5 g/dl
Results

• Planned interim analysis showed inferiority of the experimental treatment and the trial was stopped in November 2006.

• Poorer outcome in 5-year loco-regional control (59% vs. 68% (p = 0.04, RR: 1.47 [1.14-1.94]) for the Aranesp vs. control arm.

• This was also seen for the endpoint of disease-free survival (37% vs. 47%, p = 0.02, RR: 1.32 [1.04-1.68]).

• No significant difference in overall survival (40% vs. 51%, p = 0.16, RR: 1.20 [0.93-1.55]).

• There were no differences in radiation related morbidity.
Conclusions

• There is a Significant **Negative Effect** On Survival And LRC For Darbepoetin During Radiotherapy For HNC
ASCO 2009: Practical Implications in HNC

- HPV related Oropharynx; new Entity, different disease. ? Different therapy
- Sequential vs Concurrent chemoradiotherapy: Await phase III trials: Remains an open question
- Sorafenib is active in thyroid cancer: Phase III starting