HEAD and NECK CANCER
ESMO 2012 Highlights

Sandrine FAIVRE
BEAUJON – Clichy – France
sandrine.faivre@bjn.aphp.fr
Place of **EGFR inhibitors** in Head and Neck Cancer at ESMO 2012

**Operable**
- Surgery or Preservation

**Locally advanced**
- Chemoradiation +/- induction CT

**Recurrent metastatic**
- Chemotherapy + cetuximab

**Standards of care**

- **Operable**
  - *Schmitz et al.*
  - Preoperative cetuximab

- **Locally advanced**
  - *Giralt et al.*
  - CONCERT-2 panitumumab

- **Recurrent metastatic**
  - *Psyrri et al.*
  - HPV subgroups cetuximab

www.esmo2012.org
Sandrine Faivre
SPECTRUM Trial: OS by HPV Status

HPV Positive

HR = 1.00 (95%CI: 0.62 - 1.61)

p-value = 1.00

HPV Negative

HR = 0.73 (95%CI: 0.58 - 0.93)

p-value = 0.01

Quantitative interaction test p-value = 0.25
Safety and Efficacy of Cisplatin plus 5-FU and Cetuximab in HPV-positive and HPV-negative Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck (R/M SCCHN): Analysis of the Phase III EXTREME Trial

A. Psyrri*, L. Licitra, B. de Blas, I. Celik, J. B. Vermorken

*University of Athens Medical School, Attikon University Hospital, Athens, Greece
Overall Survival by p16 Status

**p16+ patients**

- CT + cetuximab (n=18)
- CT (n=23)

HR (95% CI) 0.63 (0.30–1.34)  
*p*-value 0.22

**p16− patients**

- CT + cetuximab (n=178)
- CT (n=162)

HR (95% CI) 0.82 (0.65–1.04)  
*p*-value 0.11

HRs are CT + cetuximab vs CT  
CI, confidence interval; HR, hazard ratio
A Phase 2, Randomized Trial (CONCERT-2) of Panitumumab Plus Radiotherapy Compared With Chemoradiotherapy in Patients With Unresected, Locally Advanced Squamous Cell Carcinoma of the Head and Neck

Jordi Giralt,¹ Jose Manuel Trigo,² Sandra Nuyts,³ Esat Mahmut Ozsahin,⁴ Krzysztof Skladowski,⁵ Georges Hatoum,⁶ Jean-Francois Daisne,⁷ Alicia Zhang,⁸ Kelly Oliner,⁸ Ari Vanderwalde⁸

¹Hospital Vall d’Hebron, Barcelona, Spain; ²Hospital Virgen de la Victoria, Málaga, Spain; ³UZ Gasthuisberg, Leuven, Belgium; ⁴Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; ⁵Centrum Onkologii Instytut M. Sklodowskiej-Curie, Gliwice, Poland; ⁶University of Miami, Sylvester Comprehensive Cancer Center, Miami, Florida; ⁷Clinique Ste. Elisabeth, Namur, Belgium; ⁸Amgen Inc., Thousand Oaks, California
CONCERT-2 Study Schema

Stratification factors:

- Site of primary tumor: hypopharynx / oral cavity vs oropharynx / larynx
- RT delivery modality: IMRT* vs 3D-CRT**
- Nodal status: N0 vs N+
- Tumor stage: T1-3 vs T4

Treatment Arm 1 (CRT):
Cisplatin 100 mg/m^2 days 1 and 22 + Accelerated fractionation radiotherapy

Treatment Arm 2 (PaRT):
Panitumumab 9.0 mg/kg days 1, 22, and 43 + Accelerated fractionation radiotherapy

N = 152

Amgen Trial 20062079; ClinicalTrials.gov identifier NCT00547157

*IMRT = intensity-modulated modality radiotherapy
**3D-CRT = three-dimensional conformal modality radiotherapy

Days 1 to 49

At least 2 years from randomization
Local-Regional Control

<table>
<thead>
<tr>
<th>KM estimate – % (95% CI)</th>
<th>CRT (N = 61)</th>
<th>PaRT (N = 90)</th>
<th>Difference PaRT vs CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRC at 24 months (Primary Endpoint)</td>
<td>61 (47 – 72)</td>
<td>51 (40 – 62)</td>
<td>-9 (-23 to 9)</td>
</tr>
</tbody>
</table>

Subjects at risk:
PRT
CRT

Proportion of Local Regional Control

LRC duration

HR = 1.61 (95% CI: 0.98, 2.66)
p = 0.06

- Panitumumab plus radiation (n = 90)
- Chemoradiotherapy (n = 61)
Overall Survival

HR = 1.59 (95% CI: 0.91, 2.79)

p = 0.10

Treatment Group

Panitumumab plus radiation (n = 90) vs. Chemoradiotherapy (n = 61)

Events:
- PaRT: 38 / 90 (42)
- CRT: 18 / 61 (30)

Median follow-up (weeks):
- PaRT: 135.5
- CRT: 149.0

Subjects at risk:

<table>
<thead>
<tr>
<th></th>
<th>PRT</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>90</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>84</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>83</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td>82</td>
<td>56</td>
</tr>
<tr>
<td>8</td>
<td>74</td>
<td>54</td>
</tr>
<tr>
<td>10</td>
<td>64</td>
<td>49</td>
</tr>
<tr>
<td>12</td>
<td>62</td>
<td>49</td>
</tr>
<tr>
<td>14</td>
<td>60</td>
<td>46</td>
</tr>
<tr>
<td>16</td>
<td>58</td>
<td>44</td>
</tr>
<tr>
<td>18</td>
<td>58</td>
<td>42</td>
</tr>
<tr>
<td>20</td>
<td>55</td>
<td>41</td>
</tr>
<tr>
<td>22</td>
<td>54</td>
<td>37</td>
</tr>
<tr>
<td>24</td>
<td>48</td>
<td>32</td>
</tr>
<tr>
<td>26</td>
<td>43</td>
<td>31</td>
</tr>
<tr>
<td>28</td>
<td>40</td>
<td>31</td>
</tr>
<tr>
<td>30</td>
<td>33</td>
<td>26</td>
</tr>
<tr>
<td>32</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>34</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>36</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>38</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>40</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>42</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>44</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>46</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>48</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Modulation of the peritumoral microenvironment by cetuximab: a window pre-operative study in patients with squamous cell carcinoma of the head and neck (SCCHN)

S Schmitz, M Hamoir, H Reycher, M Magremanne, B Weynand, JF Hanin, R Lhomme, Th. Duprez, N Michoux, D Rommel, M Lonneux, N Cappoen, A Gillain, JP Machiels

Centre du Cancer,
Cliniques universitaires Saint-Luc
Université catholique de Louvain
Brussels, Belgium
Primary objective: safety

<table>
<thead>
<tr>
<th></th>
<th>Grade 1-2</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=32 (pts phase I/II)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatologic (Rash)</td>
<td>29(66%)</td>
<td>3(9%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1(3%)</td>
<td>0%</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>12(37.5%)</td>
<td>0%</td>
</tr>
<tr>
<td>Hypomagnesium</td>
<td>2(6%)</td>
<td>0%</td>
</tr>
<tr>
<td>Hypophosphorus</td>
<td>5(16%)</td>
<td>0%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>2(6%)</td>
<td>0%</td>
</tr>
<tr>
<td>Nail changes</td>
<td>1(3%)</td>
<td>0%</td>
</tr>
</tbody>
</table>

Efficacy: 90% OR by PET performed before surgery

Delord et al, CCR 2007, 2010; preoperative erlotinib
29% OR by TDM & 18% OR by PET
Results: KI67 and FDG-Pet

No significant modifications of KI67 in the control group
Results: Downstream pathways

No significant modifications in the control group
Place of mTOR inhibitors in Head and Neck Cancer at ESMO 2012

Operable
Surgery or Preservation

Locally advanced
Chemoradiation +/- induction CT

Recurrent metastatic
Chemotherapy + cetuximab

Standards of care
Faivre et al. CAPRA everolimus
Grünwald et al. TEMHEAD temsirolimus
In HNSCC, the PI3K/mTOR pathway is activated >70% of tumors and yields poor prognosis.

(No RAS mutation)

**PI3k gene amplification** (40-50%) or mutation (11-40%)

**Receptor activation**

EGFR >90%

**PTEN Loss of function**: gene mutation (10-15%), deletion or promoter methylation

Temsirirolimus

Everolimus

Temsolimus is active in refractory squamous cell carcinoma of the Head and Neck (SCCHN) failing platinum-based chemotherapy and cetuximab: efficacy and toxicity data from the phase II TEMHEAD study

Clinical efficacy of temsirolimus

**Primary endpoint:** progression free survival rate at 12 weeks ($PFR_{12wks}$) >20%

<table>
<thead>
<tr>
<th></th>
<th>days</th>
<th>%</th>
<th>CI95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>$PFR_{12wks}$</td>
<td>-</td>
<td>40</td>
<td>25-55%</td>
</tr>
<tr>
<td>$OS_{12wks}$</td>
<td>-</td>
<td>66</td>
<td>49-79%</td>
</tr>
<tr>
<td>mPFS</td>
<td>56</td>
<td>-</td>
<td>36-113d</td>
</tr>
<tr>
<td>mOS</td>
<td>152</td>
<td>-</td>
<td>76-256d</td>
</tr>
</tbody>
</table>

PFR: Progression -free survival rate  
mPFS: median PFS  
mOS: median OS
Best response according to RECIST 1.0

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SD</td>
<td>19</td>
<td>55.9</td>
</tr>
<tr>
<td>PD</td>
<td>10</td>
<td>29.4</td>
</tr>
<tr>
<td>NE</td>
<td>1</td>
<td>2.9</td>
</tr>
</tbody>
</table>

4 missing (11.8%) of 34 assessable patients
Preclinical Rational, Safety, and Preliminary Efficacy Results of Weekly Everolimus, Carboplatin and Paclitaxel as an induction Therapy for Patients with Unresectable Locally Advanced Head & Neck Squamous Cell Carcinoma (CAPRA) A GERCOR-IRC Phase I/II study

S. Faivre¹, C. Dreyer¹, E. Raymond¹, J. Fayette², J.P. Delord³, M. Gatineau⁴, B. Chibaudel⁴, N. Aissat⁴, K. Slimane⁵, C. Le Tourneau⁴

¹Clichy/FR, ²Lyon/FR, ³Toulouse/FR, ⁴Paris/FR, ⁵Rueil-Malmaison/FR

www.clinicaltrials.gov (NCT01333085)
CAPRA: Clinical trial design

Phase I dose escalation: 30-50 mg/week everolimus combined with AUC2 carboplatin and 60 mg/m² paclitaxel weekly

Phase II evaluation (two stage Simon design)

- Everolimus (RD)
- Carboplatin AUC 2
- Paclitaxel 60 mg/m²

Weekly x 9 cycles

Chemoradiation therapy
## Clinical toxicity

Treatment emergent adverse events (n=28)

<table>
<thead>
<tr>
<th>Condition</th>
<th>All grade (%)</th>
<th>Grade 1-2 (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>8 (29)</td>
<td>8 (29)</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (11)</td>
<td>3 (11)</td>
<td>-</td>
</tr>
<tr>
<td>Mucositis</td>
<td>7 (25)</td>
<td>7 (25)</td>
<td>-</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (18)</td>
<td>5 (18)</td>
<td>-</td>
</tr>
<tr>
<td>Alopecia</td>
<td>5 (18)</td>
<td>5 (18)</td>
<td>-</td>
</tr>
<tr>
<td>Oedema</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>-</td>
</tr>
<tr>
<td>Asthenia</td>
<td>18 (64)</td>
<td>15 (54)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>2 (7)</td>
<td>2 (7)</td>
<td>-</td>
</tr>
<tr>
<td>Hand foot syndrome</td>
<td>2 (7)</td>
<td>2 (7)</td>
<td>-</td>
</tr>
<tr>
<td>Rash</td>
<td>11 (39)</td>
<td>11 (39)</td>
<td>-</td>
</tr>
<tr>
<td>Acneaa</td>
<td>7 (25)</td>
<td>7 (25)</td>
<td>-</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>-</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4 (14)</td>
<td>3 (11)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>
Pre- & Post-Treatment Biomarkers in Biopsies

Ki67

Baseline

Post-CAPRA

IHC

p-S6K

Baseline

Post-CAPRA

IHC

IF

Ki67 (MIB)

Positive Surface, μm²

Baseline

Post-CAPRA

$p=0.031$

p-S6K

Positive Surface, μm²

Baseline

Post-CAPRA

$p=0.01$
Waterfall plot evaluation of patients treated with CAPRA (RECIST1.1)
CAPRA shows activity in bulky necrotic SCCHN lymph nodes

Baseline

After CAPRA

Pr FAIVRE, Beaujon - CAPRA – I-19-004
CONCLUSIONS

• No definitive conclusion on the efficacy of EGFR inhibitors according to HPV +/- subgroups (p16) in R/M stages

• No added value of panitunumab versus CDDP for chemoradiation in LA stages

• Favorable safety of cetuximab in preoperative setting with evidence of functional activity using PET and translational endpoints

• Emergence of mTOR inhibitors as promising drugs to control tumor progression in R/M stages and to potentiate chemotherapy in LA stages