Systemic Treatment in Head and Neck Cancer

Jan B. Vermorken, MD, PhD
Department of Medical Oncology
Antwerp University Hospital
Edegem, Belgium

XXVII Curso Avanzado de Oncologia Medica, El Escorial
June 18, 2015
Conflict of Interest Disclosure

- Participated in Advisory Boards of:
  - AstraZeneca, Boehringer-Ingelheim, Debiopharma, Genentech, Merck-Serono, Merck Sharp & Dome Corp, Pierre Fabre, Vaccinogen

- Lecturer fee from:
  - Merck-Serono
Outline of Presentation

• Background information
• Milestones in head and neck cancer therapy
• Important recent findings
• Multidisciplinary decision making
• Systemic treatment in LA-SCCHN
  - concurrent chemoradiotherapy (CCRT)
  - Bioradiotherapy (BRT) with cetuximab
  - Sequential chemotherapy (ICT→CCRT or BRT)
• Systemic therapy in R/M-SCCHN
• Conclusions
Head and Neck Cancer
Epidemiology, risk factors and presentation

- 5-6% of all cancers (688,000 new cases in 2012; 350,000 deaths)
- > 90% squamous cell origin (Western world)
- > 50% occur in patients ≥60 years, 28% ≥70 years
- Main risk factors: tobacco, betel chewing, alcohol, HPV
- HPV associated tumors are increasing
- Localized disease 40%, regional mets 50% distant mets 10%
- 2/3 locally/regionally advanced
- Major threat: local recurrence, SPT, SFT
Milestones in Systemic Therapies (± RT) in Head and Neck Squamous Cell Cancer

1960s
- Methotrexate (ICT, CCRT)

1970s
- Bleomycin, 5-fluorouracil, cisplatin
  Combination chemotherapy regimens

1980s
- Carboplatin
  ICT (PF) for larynx preservation

1990s
- Paclitaxel, docetaxel
  Concurrent CRT becomes standard
- TPF new standard for ICT

2000s
- Targeted therapy
- Immunotherapy
Important Recent Findings

- HPV is a risk factor for OPC (a growing epidemic)
- Tumor HPV single strongest predictor of survival (OPC)
- EGFR is a second prognostic marker
- Anti-EGFR medication is getting major attention
- Expanded role of chemotherapy (CCRT, ICT)
- Improved irradiation techniques available (IMRT)
- New imaging techniques available (PET)
- Quality of life of survivors is getting more attention
The 3-year rates of overall survival were 93.0% (95% CI, 88.3 to 97.7) in the low-risk group, 70.8% (95% CI, 60.7 to 80.8) in the intermediate-risk group, and 46.2% (95% CI, 34.7 to 57.7) in the high-risk group.

High levels of EGFR and TGFα result in reduced disease-free and overall survival.

Grandis et al, 1998
Diagnosis and Treatment of SCCHN: A Multidisciplinary Challenge

Patient management

- Surgery
- Chemotherapy
- Combination therapy
- Imaging of response
- Radiotherapy
- Immunotherapy
- Postoperative treatment
- Diagnostic markers
- Prognostic markers
- Efficacy
- Quality of life
Decision Making during MDT Meetings

SCCHN patients

• Disease factors (e.g. site, stage, biology [HPV, EGFR], specific risk factors for locoregional or distant relapse)

• Patient factors (e.g. age, sex, performance status, nutritional status, comorbid chronic disease, oral health, lifestyle habits, socio-economic status)

• Treatment factors (surgery, radiotherapy, chemotherapy, immunotherapy, targeted therapy)

• What do patients want?
Treatment Options in SCCHN
Standard Treatment

- Early-stage SCCHN (stage I-II)
  - ERT vs BT vs S (depending on patient/disease factors)\(^1\)

- Locoregionally advanced SCCHN (stages III-IV)
  - Surgery → adjuvant RT or concurrent CRT (CCRT)
  - Definitive CCRT (surgery remains an option)
  - Definitive cetuximab/RT (surgery remains an option)
  - Induction chemotherapy (ICT) → local treatment

- Recurrent/metastatic SCCHN
  - Recurrent resectable: postop. RT or CCRT\(^3\)
  - R/M-SCCHN: PFE (fit patients); single drug (PS2), BSC\(^2\)

---
## Clinical Practice Guidelines for Patients with Locoregionally Advanced SCCHN
### Standard options

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery → RT or CCRT</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Concomitant CT and RT*</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Cetuximab plus RT</td>
<td>II</td>
<td>B</td>
</tr>
<tr>
<td>CCRT or ICT → RT for organ preservation</td>
<td>II</td>
<td>A</td>
</tr>
<tr>
<td>ICT → CCRT (sequential therapy)</td>
<td>Still under evaluation</td>
<td></td>
</tr>
</tbody>
</table>

*in case of mutilating surgery and in nonresectable disease
NCCN (US) Guidelines for LA SCCHN
Level of evidence

**Squamous Cell Cancers**

**Lip, Oral Cavity, Oropharynx, Hypopharynx, Glottic Larynx, Supraglottic Larynx, Ethmoid Sinus, Maxillary Sinus, Occult Primary:**

- **Primary systemic therapy + concurrent RT**
  - High-dose cisplatin\(^3,4\) (preferred) (category 1)
  - Cetuximab\(^5\) (category 1)
  - Carboplatin/infusional 5-FU (category 1)\(^6,7\)
  - 5-FU/hydroxyurea\(^8\)
  - Cisplatin/paclitaxel\(^9\)
  - Cisplatin/infusional 5-FU\(^9\)
  - Carboplatin/paclitaxel\(^10\) (category 2B)
  - Weekly cisplatin 40 mg/m\(^2\) (category 2B)\(^11,12\)
  - Postoperative chemoradiation:
    - Cisplatin\(^13-17\) (category 1 for high risk)

**Note:** All recommendations are category 2A unless otherwise indicated.

---

**NCCN Guidelines Version 2.2014**
Head and Neck Cancers

---

**PRINCIPLES OF SYSTEMIC THERAPY**

The choice of chemotherapy should be individualized based on patient characteristics (PS, goals of therapy).

- The standard chemoradiation approach for FRT patients with locally advanced disease remains concurrent cisplatin and radiotherapy.
- Cisplatin-based induction chemotherapy can be used, followed by radiation-based locoregional treatment (e.g., sequential chemorT).
  - However, an improvement in overall survival with the incorporation of induction chemotherapy compared to proceeding directly to state of the art concurrent chemorT (cisplatin preferred, category 1) has not been established. Randomized phase III studies comparing sequential chemotherapy/RT to concurrent chemotherapy/RT alone are ongoing and have not demonstrated a convincing survival benefit with the incorporation of induction chemotherapy.
- Cisplatin-based induction chemotherapy followed by high-dose, every-3-week cisplatin chemoradiotherapy is not recommended due to toxicity concerns.\(^1,2\)
- After induction chemotherapy, multiple options can be used for the radiation-based portion of therapy. Radiotherapy alone versus radiotherapy plus weekly carboplatin or cetuximab are among the options.
CRT: Late Toxicity

- Analysis of 230 patients receiving CRT in 3 studies (RTOG 91-11, 97-03, 99-14)

MVA: significant variables correlating with severe late toxicity were: older age (OR, 1.05 per year; p=.001), advanced T-stage (OR, 3.07; p=.0036), larynx/hypopharynx primary site (OR, 4.17; p=.0041) and neck dissection (OR, 2.39; p=.018)

Methods to Reduce the Toxicity of Cisplatin-based CCRT in SCCHN

Better targeting of RT
- CT – MRI – (PET)
- IGRT

New radiotherapy techniques
- IMRT and SW-IMRT
- Stereotactic radiotherapy
- IMPT

Alternatives for cisplatin
- Other cisplatin dose or schedules
- Other cytotoxics (carboplatin, taxanes, low-dose gemcitabine)
- Biological agents (cetuximab)

CT= computed tomography; MRI= magnetic resonance imaging; IGRT= image-guided RT; IMPT intensity-modulated particle therapy; IMRT= intensity-modulated RT; PET= positron emission tomography; RT= radiotherapy
Alternatives for High-Dose Cisplatin in CCRT: How strong is the evidence

- 100 mg/m² q 3 wks recommended as radio-enhancer in CCRT studies with cisplatin¹
- Modeling studies suggest more benefit with more frequent administrations during RT²,³
- A minimum cumulative dose of 200 mg/m² has been generally accepted as sufficient for an adequate enhancing effect⁴,⁵
- Weekly 40 mg/m²/wk may induce more mucositis⁶,⁷,⁸,⁹
- QoL was worse with the weekly regimen⁹

Differential Impact of Cisplatin Dose Intensity on HPV+ and HPV- LA-SCCHN

Retrospective review of newly diagnosed HNSCC patients from 2000-2012, who had been treated with cisplatin-based chemoradiotherapy, and in whom the HPV status had been ascertained.

659 patients identified
- 404 HPV+ (95% OPC)
- 255 HPV- (38% OPC)

Predictors of overall survival were identified in the HPV+ and HPV- patients including total cisplatin dose given (>200 mg/m² vs. <200 mg/m²)

*ASCO abstract #6020: Spreafico et al (PMH, Toronto, Canada & INT, Milan Italy)
Abstract #6020: Overall Survival by Cisplatin Dose

Observation confirmed in a multivariable analysis
Abstract #6019: Utilization and Outcomes of Low Dose vs. High Dose Cisplatin in Head and Neck Cancer Patients Receiving Concurrent Radiation Therapy (RT)

Stuart J. Wong, Li Li, Lisa M Hess, Amy Chen, Walter J. Curran, P. Harari, Randal Kimple, Barbara A. Murphy, Laura Opincar, and Adam S. Garden

Longitudinal Oncology Registry of Head and Neck Carcinoma (LORHAN)
Patients treated between 2005-2010
In total 334 patients received the weekly low dose and 757 the 3-weekly high dose
Abstract #6019.
High-Dose vs Low-Dose CDDP: Overall Survival

P<0.001

Abstract #6019. Wong et al
Conclusions on Cisplatin Dose at ASCO 2015*

- Total cisplatin dose is important. Not surprisingly, the effect is less apparent in good prognosis patients.
- Low dose weekly regimens may result in lower total cisplatin dose than with the high-dose 3-weekly schedule.
- Greater toxicity with high-dose schedule not demonstrated.

⇒ Low-dose weekly regimen may end up with inferior results.

- This suggest a need for caution before adopting LD-weekly cisplatin as a treatment standard.

*Discussant  David Adelstein
## Can Carboplatin Replace Cisplatin in CCRT?

### No large randomized trials

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Study</th>
<th># Patients</th>
<th>Toxicity</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilkins 2013¹</td>
<td>Marched-pair analysis</td>
<td>65 Cis-Pt</td>
<td>Emesis ↓ with Cb</td>
<td>LRC, DM, OS at 3 years comparable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65 Carbo-Pt</td>
<td>BM toxicity↑ with Cb</td>
<td></td>
</tr>
<tr>
<td>Fountzilas 2004</td>
<td>Phase III</td>
<td>124 patients</td>
<td>N/V more in B</td>
<td>TTP and OS longer with B &amp; C : at 3 years</td>
</tr>
<tr>
<td></td>
<td>A - RT</td>
<td></td>
<td>BM tox. ↑ in B/C</td>
<td>A: 17.5%</td>
</tr>
<tr>
<td></td>
<td>B –RT + Cis-Pt</td>
<td></td>
<td></td>
<td>B: 52%</td>
</tr>
<tr>
<td></td>
<td>C – RT + Carbo-Pt</td>
<td></td>
<td></td>
<td>C: 42%</td>
</tr>
<tr>
<td>Chitapanarux 2007</td>
<td>Phase III single center</td>
<td>206 patients</td>
<td>Renal tox., WBC↓, Hb↓ with Cis-Pt</td>
<td>3-yr OS 77.7% (Cis)</td>
</tr>
<tr>
<td></td>
<td>in NPC</td>
<td>101 Cis-Pt</td>
<td></td>
<td>3-yr OS 79.2% (Cb)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>105 Carbo-Pt</td>
<td>PLT↓ with Carbo-Pt</td>
<td></td>
</tr>
<tr>
<td>Li et al 2015*</td>
<td>Meta-analysis</td>
<td>1165 patients, including NPC</td>
<td>More NHTOX with CDDP</td>
<td>CIS vs CARBO showed HR 0.67 (95% CI 0.49-0.91, p=0.01)</td>
</tr>
</tbody>
</table>

*ASCO 2015
Can Cetuximab Replace Cisplatin in CCRT?

<table>
<thead>
<tr>
<th>50 trials, 9615 pts (MA)*</th>
<th>1 trial, 424 patients (Bonner et al)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR of death <strong>0.74</strong> (<strong>0.67-0.82)</strong>†</td>
<td>HR of death <strong>0.74</strong> (<strong>0.57-0.97)</strong></td>
</tr>
<tr>
<td>Main effect on local failure</td>
<td>Only effect on local failure</td>
</tr>
<tr>
<td>Modest effect on DM</td>
<td>No effect on DM</td>
</tr>
<tr>
<td>Efficacy irrespective of site and of fractionation schedule</td>
<td>Effect may be site and RT schedule specific</td>
</tr>
<tr>
<td>Significant acute toxicity which may inflict on late toxicity, in particular swallowing dysfunction</td>
<td>Grade 3-4 mucositis and radiation dermatitis not significantly increased. Late toxicity seems not increased. High compliance. QoL BRT ~ RT†</td>
</tr>
</tbody>
</table>

## Chemoradiation and Bioradiation (cetuximab)

### A meta-analysis of published data

Search in PubMED, EMBASE, SCOPUS, Web of Science and the Cochrane Register of Controlled Trials

Included were 15 studies and 1,808 patients

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>CCRT</th>
<th>RT+CET</th>
<th>Risk Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-yr OS</td>
<td>71.0%</td>
<td>60.7%</td>
<td>0.66 (0.46-0.94), p=0.02</td>
</tr>
<tr>
<td>2-yr DFS</td>
<td>61.7%</td>
<td>43.1%</td>
<td>0.68 (0.53-0.87), p=0.002</td>
</tr>
<tr>
<td>2-yr LRR</td>
<td>19.6%</td>
<td>32.3%</td>
<td>0.63 (0.45-0.87), p=0.005</td>
</tr>
</tbody>
</table>

*Barni et al, ASCO 2014 (abstr.#6014)*
TPF: A Breakthrough in Induction Chemotherapy

- **More efficacious** (PFS, OS, larynx preservation)
  - Posner MR et al. with TAX 324 (NEJM 2007)
  - Vermorken JB et al with TAX 323 (NEJM 2007)
  - Pointreau Y et al. with TAX 323 regimen (JNCI 2009)

- **Less toxic** (less G3-4 PLT↓, nausea/vomiting, stomatitis, hearing loss and toxic death)

- **Better quality of life**
  - Van Herpen et al, BJC 2010; 103: 1173-1181

- **Cost-effective**
Important Questions Raised after TPF Studies
Locoregionally advanced SCCHN

• Do some patients respond better to ICT and RT than others?

• Is ICT→RT alone equivalent or superior to CCRT?

• Do ICT and CCRT have complementary effects on overall control of disease?*

• Is induction TPF followed by CCRT superior to CCRT alone?

• Can TPF be further improved by targeted therapy?

* Supported by MACH-NC
### Randomized Trials of Sequential Therapy versus Concurrent Chemoradiation Only

<table>
<thead>
<tr>
<th>Group</th>
<th>Regimen</th>
<th>Survival benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTCC (Sp)(^1)</td>
<td>TPF (or PF) x 3 → CCRT (P)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>CCRT (cisplatin)</td>
<td></td>
</tr>
<tr>
<td>Boston (US)(^2)</td>
<td>TPF x 3 → CCRT (C or TAX)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>CCRT (cisplatin)</td>
<td></td>
</tr>
<tr>
<td>Chicago (US)(^3)</td>
<td>TPF x 2 → CCRT (THFX)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>CCRT (THFX)</td>
<td></td>
</tr>
<tr>
<td>GCTCC (It)(^4)</td>
<td>CCRT (PF) w/wo foregoing TPF</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>BRT (Cetuximab) w/wo foregoing TPF</td>
<td></td>
</tr>
</tbody>
</table>


\(^3\)Cohen et al, ASCO 2012 (abstr. #5501); \(^4\)Ghi et al, ASCO 2013 (abstr. #6003) and ASCO 2014 (abstr. #6004)
Treatment of HPV Positive OPC

- No guidelines (NCCN)
- Proposed strategies
  A. The use of induction chemotherapy
     - OPC chemosensitive → predicts outcome
     - HPV+ subset of OPC often high N stage
  B. Treatment deintensification*
     - Reduced RT dose (ECOG 1308; Quarterback trial)$^{1,2}$
     - RT alone, rather than CCRT (ADEPT trial)$^3$
     - Bioradiation with cetuximab (RTOG 1016; DeESCALaTE)

*Candidates for that seems most likely T1-3 and N0-2a stage disease (Quon & Forastiere, 2013)

$^1$ Stage III-IVB resectable HPVOPC: 3x TCE, when CR-54Gy/27 fr, when PR/SD=69.3 Gy/33fr

$^2$ Stage III and IV HPVOPC: 3x TPF, when CR/PR randomization between 56 Gy and 70 Gy, when NR standard CCRT

$^3$ TORS for T1-4a, N+ (ECE+) HPVOPC, negative margins: RT vs CCRT with cisplatin
E1308: Phase II Study Schema

**Induction Chemotherapy**
- Eligibility
  - OPSCC
  - HPV ISH + and / or p16+
  - Stage III, IVA,B
- **Cisplatin** 75mg/m² D1
- **Paclitaxel** 90mg/m² D1,8,15
- **Cetuximab** 250mg/m² D1,8,15
- Q 21 days for 3 cycles

**Concurrent Chemoradiation**
- **CLINICAL CR**
  - Low dose IMRT 54Gy/27fx* + Cetuximab weekly
- **CLINICAL PR /SD**
  - Full dose IMRT 69.3Gy/33fx* + Cetuximab weekly

Cmelak et al. ASCO 2015
Concurrent Cetuximab and a Lower Dose of Definitive Radiation: Successfully Used in Complete Responders to Induction CT

Cmelak et al. ASCO 2014
## Selected, Meaningful (score ≥ 2/10) 12 Month Toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>High Dose (n=9)</th>
<th>Low Dose (n=35)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mouth Pain</strong></td>
<td>1 (25%)</td>
<td>2 (6%)</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>General Pain</strong></td>
<td>2 (50%)</td>
<td>8 (27%)</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>Swallowing solids</strong></td>
<td>5 (100%)</td>
<td>11 (35%)</td>
<td><strong>0.012</strong></td>
</tr>
<tr>
<td><strong>Nutrition</strong></td>
<td>2 (40%)</td>
<td>2 (6%)</td>
<td>0.084</td>
</tr>
<tr>
<td><strong>Taste &amp; Smell</strong></td>
<td>2 (50%)</td>
<td>11 (37%)</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>Voice</strong></td>
<td>1 (25%)</td>
<td>4 (13%)</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Teeth</strong></td>
<td>1 (33%)</td>
<td>5 (17%)</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Composite (swallowing solids, dry mouth, taste/smell)</strong></td>
<td>100%</td>
<td>70%</td>
<td></td>
</tr>
</tbody>
</table>

Other toxicities not reduced (e.g. swallowing liquids, excessive mucous)
Treatment Options in SCCHN

Standard Treatment

• Early-stage SCCHN (stage I-II)
  - ERT vs BT vs S (depending on patient/disease factors)\(^1\)

• Locoregionally advanced SCCHN (stages III-IV)
  - Surgery → adjuvant RT or concurrent CRT (CCRT)
  - Definitive CCRT (surgery remains an option)
  - Definitive cetuximab/RT (surgery remains an option)
  - Induction chemotherapy (ICT) → local treatment

• Recurrent/metastatic SCCHN
  - Recurrent resectable: postop. RT or CCRT\(^3\)
  - R/M-SCCHN: PFE (fit patients); single drug (PS2), BSC\(^2\)

\(^3\)Strojan et al. Head & Neck- DOI 10.1002/hed.23542
### First-line Treatment with Anti-EGFR MoAbs

#### Randomized II/III trials in R/M-SCCHN

<table>
<thead>
<tr>
<th>Study/Reference</th>
<th>N</th>
<th>Regimen</th>
<th>RR (%)</th>
<th>PFS (mo)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG 5397 Burtness et al J Clin Oncol 2005</td>
<td>117</td>
<td>Cisplatin + cetuximab</td>
<td>26&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.2</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin + placebo</td>
<td>10</td>
<td>2.7</td>
<td>8.0</td>
</tr>
<tr>
<td>EXTREME Vermorken et al N Engl J Med 2008</td>
<td>442</td>
<td>PF&lt;sup&gt;1&lt;/sup&gt; + cetuximab</td>
<td>36&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10.1&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PF&lt;sup&gt;1&lt;/sup&gt;</td>
<td>20</td>
<td>3.3</td>
<td>7.4</td>
</tr>
<tr>
<td>SPECTRUM Vermorken et al Lancet Oncol 2013</td>
<td>657</td>
<td>PF&lt;sup&gt;2&lt;/sup&gt; + panitumumab</td>
<td>36&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>11.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PF&lt;sup&gt;2&lt;/sup&gt;</td>
<td>25</td>
<td>4.6</td>
<td>9.0</td>
</tr>
</tbody>
</table>

PF<sup>1</sup> = cisplatin or carboplatin plus 5-FU; PF<sup>2</sup> = cisplatin plus 5-FU

<sup>a, b, c</sup>: significant differences
EXTREME – Overall Survival
Long-term follow-up

Vermorken et al. ASCO 2014 (abstr. #6021)
<table>
<thead>
<tr>
<th>Author</th>
<th>Phase</th>
<th>N</th>
<th>Regimen</th>
<th>ORR (%)</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vermorken</td>
<td>III</td>
<td>442</td>
<td>PF</td>
<td>20</td>
<td>3.3</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PF + cetuximab</td>
<td>36*</td>
<td>5.6*</td>
<td>10.1*</td>
</tr>
<tr>
<td>Burtness</td>
<td>III</td>
<td>117</td>
<td>Cis + Placebo</td>
<td>10</td>
<td>2.7</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cis + cetuximab</td>
<td>26*</td>
<td>4.2</td>
<td>9.2</td>
</tr>
<tr>
<td>Buentzel</td>
<td>II</td>
<td>23</td>
<td>Pacli/Carbo + cetuximab</td>
<td>56</td>
<td>5.0**</td>
<td>8.0</td>
</tr>
<tr>
<td>Hitt</td>
<td>II</td>
<td>46</td>
<td>Pacli + cetuximab</td>
<td>54</td>
<td>4.2</td>
<td>8.1</td>
</tr>
<tr>
<td>Guigay</td>
<td>II</td>
<td>54</td>
<td>Doce/Cis /cetuximab</td>
<td>54</td>
<td>7.1</td>
<td>15.3</td>
</tr>
</tbody>
</table>

*Significant; **TTP
Vermorken et al. NEJM 2008; Burtness et al. JCO 2005;
TPExtreme TRIAL - GORTEC 2014-01
PI: J Guigay

Control arm (EXTREME)
(6 cycles every 3 weeks)
- Cisplatin: 100 mg/m² iv
- 5FU: 4000 mg/m² during 96h in continuous infusion
- Cetuximab: 400 mg/m² iv (loading dose), then 250 mg/m² iv

Experimental arm (TPEx)
(4 cycles every 3 weeks)
- Cisplatine: 75 mg/m² iv
- Docetaxel: 75 mg/m² iv
- Cetuximab: 400 mg/m² iv (loading dose), then 250 mg/m² iv
- + G CSF after each cycle

- Cetuximab weekly until progression or unacceptable toxicity
- Cetuximab every 2 weeks until progression or unacceptable toxicity

Phase II
(R 1:1)
Minimization on: PS
Metastatic status, Previous cetuximab
Country

SCCHN
R/M 1st line
(N = 416)
✓ Age < 71 y
✓ PS < 2
✓ Previous: cddp < 300mg/m²
anti-EGFR > 1y

✓ Primary objective: OS
✓ Ancillary studies: QOL, cost-effectiveness, p16 / HPV tumor status

N = 270
R

N = 270
### 1st/2nd Line Treatment with Anti-EGFR Drugs
Randomized phase III trials in R/M-SCCHN

<table>
<thead>
<tr>
<th>Study/Reference</th>
<th>N</th>
<th>Regimen</th>
<th>RR (%)</th>
<th>PFS</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMEX</td>
<td>486</td>
<td>Gefitinib (250 mg)</td>
<td>3</td>
<td>ND</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gefitinib (500 mg)</td>
<td>8</td>
<td>ND</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methotrexate</td>
<td>4</td>
<td>ND</td>
<td>6.7</td>
</tr>
<tr>
<td>ECOG 1302</td>
<td>270</td>
<td>D + Gefitinib</td>
<td>12</td>
<td>3.5 (TTP)</td>
<td>7.3</td>
</tr>
<tr>
<td>Argiris et al, 2013</td>
<td></td>
<td>D + placebo</td>
<td>6</td>
<td>2.1 (TTP)</td>
<td>6.0</td>
</tr>
<tr>
<td>ZALUTE</td>
<td>286</td>
<td>Z + BSC (-MTX)</td>
<td>6</td>
<td>2.3*</td>
<td>6.7°</td>
</tr>
<tr>
<td>Machiels et al, 2010</td>
<td></td>
<td>BSC (optional MTX)</td>
<td>1</td>
<td>1.9*</td>
<td>5.2°</td>
</tr>
<tr>
<td>LUX HN1</td>
<td>483</td>
<td>Afatinib</td>
<td>10</td>
<td>2.6**</td>
<td>6.8</td>
</tr>
<tr>
<td>Machiels et al, 2015</td>
<td></td>
<td>Methotrexate</td>
<td>6</td>
<td>1.7**</td>
<td>6.0</td>
</tr>
</tbody>
</table>

BSC = best supportive care; Z = zalutumumab; MTX = methotrexate; ND = no data; TTP = time to progression

*HR (95% CI): 0.62 (0.47-0.83), p=0.0010; ** HR (95% CI): 0.77 (0.57-1.05), p=0.0648; ° HR (95% CI): 0.80 (0.65-0.98)
Other Novel Targeted Agents in SCCHN

- Anti-angiogenesis
  - VEGF
  - VEGFR
- Integrin inhibitors
- Histone deacetylase inhibitors
  - No phase III
- PI3K/Akt/mTOR pathway inhibitors
  - Data available
- Proteasome inhibitors
- IGFR inhibitors
- SRC inhibitors
Expression of PD-L1 on
a) tumor cells &
b) macrophages

In mouse models antibodies **blocking PD-1 / PD-L1 interaction** lead to tumor rejection.

Clinical prognosis correlates with presence of TILs and PD-L1 expression in multiple cancers.
HNSCC expansion cohort of the KEYNOTE-012 Nonrandomized, Phase 1b Multi-cohort trial*

Patients:
• Recurrent or metastatic HNSCC, regardless of PD-L1 or HPV status
• Have measurable disease based on RECIST 1.1
• ECOG performance status of 0 or 1

Response assessment: Every 8 weeks
Primary end points: ORR per modified RECIST v1.1 by investigator review; safety
Secondary end points: PFS, OS, duration of response

Pembrolizumab 200 mg Q3W

• Treatment for 24 months†
• Documented disease progression‡
• Intolerable toxicity

*Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
†Treatment beyond progression was allowed.
‡Re-treatment was permitted.

Presented by: Tanguy Seiwert
## Overall Response Rate [Site Radiology Review]*

<table>
<thead>
<tr>
<th>Best overall response</th>
<th>Total N = 117†</th>
<th>HPV+ n = 34</th>
<th>HPV− n = 81</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>95% CI</td>
<td>n (%)</td>
</tr>
<tr>
<td>ORR</td>
<td>29 (24.8)</td>
<td>17.3-33.6</td>
<td>7 (20.6)</td>
</tr>
<tr>
<td>Complete Response</td>
<td>1 (0.9)</td>
<td>0.0-4.7</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>28 (23.9)</td>
<td>16.5-32.7</td>
<td>6 (17.6)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>29 (24.8)</td>
<td>17.3-33.6</td>
<td>9 (26.5)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>48 (41.0)</td>
<td>32.0-50.5</td>
<td>13 (38.2)</td>
</tr>
<tr>
<td>No Assessment#</td>
<td>9 (7.7)</td>
<td>3.6-14.1</td>
<td>4 (11.8)</td>
</tr>
<tr>
<td>Non-evaluable±</td>
<td>2 (1.7)</td>
<td>0.2-6.0</td>
<td>1 (2.9)</td>
</tr>
</tbody>
</table>

*Unconfirmed and confirmed RECIST v 1.1 responses
†Includes patients who received ≥1 dose of pembrolizumab, had measurable disease at baseline and ≥1 postbaseline scan or discontinued due to PD or DRAE. 15 patients not included in this analysis: 2 did not have baseline scans within screening window, 13 did not have post-baseline assessment and discontinued due to non-drug related AE (7), subject withdrawal of consent (4), other (2).
#No assessment: Discontinued without post-baseline radiographic assessment due to drug related AE (2 patients), clinical PD (6 patients), death due to PD (1 patient)
±Non-evaluable: Images were not of sufficient quality to be evaluable
HPV status missing for 2 patients with oropharynx cancer. Cancers outside the oropharynx are considered HPV negative by convention.
Data cutoff date: March 23, 2015.

Presented by: Tanguy Seiwert
Conclusions at ASCO 2015

• Largest experience of immunotherapy in head and neck cancer (N =132 patients)

• 56% of patients experienced any decrease in target lesions
  o Response rate of 25%
  o Broadly active in both HPV(+) and HPV(-) patients
  o Active in heavily pretreated population
  o Responses were durable ➔ 86% of responding patients remain in response

• Pembrolizumab administered at a fixed dose of 200 mg every 3 weeks was well tolerated

• Novel signature biomarkers are promising (related abstract #6017)

• Pembrolizumab is currently being evaluated in two phase III trials to investigate the clinical benefit of pembrolizumab vs standard of care chemotherapy (using the 200mg every 3 week dose schedule)