Present and Future of Head and Neck Cancer Therapy  
(Focus at systemic therapy)  

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1st Hellenic Conference on Head and Neck Cancer, organized by the Hellenic Society of Head and Neck Oncology (HeSHNO), Athens, October 21-22, 2017
Conflict of Interest Disclosure

• Participates in Advisory Boards of:
  Amgen, AstraZeneca, Boehringer Ingelheim, Innate Pharma, Merck KGaA, Merck Sharp & Dome Corp, PCI Biotech, Synthon Biopharmaceuticals, Vaccinogen

• Lecturer fee from:
  Merck-Serono, Vaccinogen
Head and Neck Cancer (HNC)  
Introduction

- A changing population
  - Incidence of elderly patients increasing

- A changing disease
  - Incidence of viral induced tumors increasing

- A changing treatment approach
  - Surgery (reconstruction, organ sparing, TORS)
  - Radiation (fractionation, targeting, technique, CRT, BRT)
  - Systemic (cytotoxics, targeted agents, immunotherapy)

- Multidisciplinary Team (MDT) meetings
  - Patient centered approach
Treatment Strategies in Locoregionally Advanced SCCHN

- Definitive CCRT (planned or optional surgery [PS or OpS])\(^1\)*
- Surgery → adjuvant RT or concurrent CRT (CCRT)\(^1\)
- Altered fractionation radiotherapy (PS or OpS)\(^2\)*
- Hypoxic modification of radiotherapy (PS or OpS)\(^3\)*
- Definitive RT + cetuximab (BRT; with PS or OpS)
- TPF induction CT → definitive local therapy (RT, CCRT, BRT)

\(^1\)MACH-NC meta-analysis; \(^2\)MARCH meta-analysis; \(^3\)DAHANCA meta-analysis (*all 3 approaches have level IA evidence)

CCRT = chemoradiation with cisplatin; BRT = bioradiation
## Clinical Practice Guidelines for Patients with Locoregionally Advanced SCCHN

<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></td>
<td>Still under evaluation</td>
</tr>
</tbody>
</table>

*in case of mutilating surgery and in nonresectable disease ; **Cisplatin dose: 100 mg/m² x3 during CF-RT**

USA NCCN 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\(^8\)
  ➢ 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.
Conclusion on Cisplatin Dose: ASCO 2015*

- Total cisplatin dose (TD-DDP) is important.
- Effect less apparent in HPV(+) patients
- Low dose weekly cisplatin (LD-DDP) regimens may result in lower TD-DDP than with the HD-DDP 3 weekly
- 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-DDP weekly cisplatin as a treatment standard

\[^1\text{Spreafico et al. Abstract #6020, ASCO 2015)}\]
\[^2\text{Wong et al. Abstract #6021, ASCO 2015)}\]
\[^*\text{Discussant David Adelstein}\]
CCRT: Late Toxicity

• Analysis of 230 patients receiving CCRT 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)

CCRT Standard Nonsurgical Therapy

What next in LA-SCCHN?

- Should all patients be treated with CCRT?
- Is further treatment intensification feasible and worth considering?
  - adding more cytotoxic chemotherapy (ICT)
  - adding targeted therapy
  - adding a hypoxic sensitizer to CCRT
  - immunotherapy
- Can we select patient who might need less intensive therapy (de-escalation of locoregional therapy)?
Multidisciplinary Team (MDT) Meetings

- Head and neck surgeon
- Radiation oncologist
- Medical oncologist
- Anesthesiologist, internist, general practitioner
- Biologist, pathologist
- Radiologist
- Social worker, psychologist
- Speech therapist
- Dietician

Guidelines Clinical trials
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, comorbidities, oral health, lifestyle habits, socio-economic status [marital status])

- **Treatment factors** (surgery, radiotherapy, chemotherapy, immunotherapy, targeted therapy)

- **Communication / information / support / taking into account the wish of the patient**
Effectiveness of Chemoradiation in HNC in an Older Patient Population*

SEER Database

- The unadjusted multivariate Cox regression model for the entire cohort demonstrated no benefit for CCRT over RT (HR 1.134, 95% CI: 1.017-1.203, P<.001)

- Significantly associated with overall survival were:
  - Comorbidities
  - Medicare eligibility
  - Stage
  - Lymph node status
  - IMRT receipt
  - Marital status
  - Cancer site
  - Grade
  - Diagnostic era
  - Age

* VanderWalde et al. Int J Radiation Oncol Biol Phys 2014: 89: 30-37 (10,599 patients treated outside randomized control setting. SEER-Medicare linked database (1992-2007) : 68% male, 89% white, 54% no comorbidities, 55% married. 74% were treated with RT, 26% with CCRT
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.

Randomized Trials of CCRT vs BRT

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Drug (exp)</th>
<th>Comparator</th>
<th>Phase (no pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT 1302834</td>
<td>USA</td>
<td>Cetuximab</td>
<td>Cisplatin</td>
<td>III (987)&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>NCT 01874171</td>
<td>UK</td>
<td>Cetuximab</td>
<td>Cisplatin</td>
<td>III (304)&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>NCT 01855451</td>
<td>Australia</td>
<td>Cetuximab</td>
<td>Cisplatin</td>
<td>III (200)&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>NCT 00169247</td>
<td>France</td>
<td>Cetuximab</td>
<td>Cisplatin</td>
<td>II (156)&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>NCT 00716391</td>
<td>Spain</td>
<td>Cetuximab</td>
<td>Cisplatin</td>
<td>III (458)&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>NCT 00547157</td>
<td>“Concert 2”</td>
<td>Panitumumab</td>
<td>Cisplatin</td>
<td>II (150)</td>
</tr>
<tr>
<td>NCT 00820248</td>
<td>Canada</td>
<td>Panitumumab</td>
<td>Cisplatin</td>
<td>III (320)&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup>in HPV(p16)+OPC (RTOG-1016); <sup>2</sup>De-Escalate study in HPV(p16)+OPC; <sup>3</sup>TROG 12.01 study in HPV(p16)+OPC; <sup>4</sup>Tremplin (after TPF); <sup>5</sup>after TPF; <sup>6</sup>Af (in exp. arm) vs SF (comparator);
CCRT Standard Nonsurgical Therapy
What next in LA-SCCHN

• Should all patients be treated with concurrent CRT?

• Is further treatment intensification feasible and worth considering?
  - adding more cytotoxic chemotherapy (ICT)
  - adding targeted therapy
  - adding a hypoxic sensitizer to concurrent CRT
  - immunotherapy

• Can we select patient who might need less intensive therapy (de-escalation of locoregional therapy)?
## Randomized Trials of Sequential Therapy versus Concurrent Chemoradiation Only

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

# Randomized Trials of CCRT ± EGFR Inhibition

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Anti-EGFR</th>
<th>CCRT (drug)</th>
<th>Phase (no pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT 00265941</td>
<td>USA</td>
<td>Cetuximab</td>
<td>Cisplatin</td>
<td>III (895)¹</td>
</tr>
<tr>
<td>NCT 01301248</td>
<td>Greece</td>
<td>Cetuximab</td>
<td>Cisplatin</td>
<td>II (80)</td>
</tr>
<tr>
<td>NCT 00496652</td>
<td>Denmark</td>
<td>Zalutumumab</td>
<td>Cisplatin</td>
<td>III (619)</td>
</tr>
<tr>
<td>NCT 00500760</td>
<td>Concert-1</td>
<td>Panitumumab</td>
<td>Cisplatin</td>
<td>II (153)</td>
</tr>
<tr>
<td>NCT 00229723</td>
<td>International</td>
<td>Gefitinib</td>
<td>Cisplatin</td>
<td>II (224)²</td>
</tr>
<tr>
<td>NCT 00410826</td>
<td>USA</td>
<td>Erlotinib</td>
<td>Cisplatin</td>
<td>II (204)</td>
</tr>
<tr>
<td>NCT 01074021</td>
<td>China</td>
<td>Nimotuzumab</td>
<td>Cisplatin</td>
<td>III (480)³</td>
</tr>
<tr>
<td>NCT 00957086</td>
<td>Singapore</td>
<td>Nimotuzumab</td>
<td>Cisplatin</td>
<td>III (710)⁴</td>
</tr>
<tr>
<td>NCT 01516996</td>
<td>China</td>
<td>Nimotuzumab</td>
<td>TP</td>
<td>II (80)⁵</td>
</tr>
</tbody>
</table>

¹RTOG0522; ²published (no effect); ³study (placebo-controlled) in NPC (2008 stages III/IVa); ⁴placebo controlled in the postoperative setting; ⁵nimotuzumab during 2x ICT and CRT
# Hypoxic Modification of Radiotherapy in SCCHN

## Head and neck cancer - meta analysis - summary

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Events / Total</th>
<th>Odds ratio and 95% CI</th>
<th>Odds ratio</th>
<th>Risk Reduction</th>
<th>NNT**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypoxic modification</td>
<td>Control</td>
<td>Odds ratio</td>
<td>Risk Reduction</td>
<td>NNT**</td>
</tr>
<tr>
<td>Loco-regional control</td>
<td>1203 / 2406</td>
<td>1383 / 2399</td>
<td>0.71 (0.63-0.80)*</td>
<td>8% (5-10%)*</td>
<td>13</td>
</tr>
<tr>
<td>Disease specific survival</td>
<td>1175 / 2335</td>
<td>1347 / 2329</td>
<td>0.73 (0.64-0.82)</td>
<td>7% (5-10%)</td>
<td>14</td>
</tr>
<tr>
<td>Overall survival</td>
<td>1450 / 2312</td>
<td>1519 / 2305</td>
<td>0.87 (0.77-0.98)</td>
<td>3% (0-6%)</td>
<td>31</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>159 / 1427</td>
<td>179 / 1391</td>
<td>0.87 (0.69-1.09)</td>
<td>2% (-1-4%)</td>
<td>57</td>
</tr>
<tr>
<td>Radiotherapy complications</td>
<td>307 / 1864</td>
<td>297 / 1822</td>
<td>1.00 (0.82-1.23)</td>
<td>0% (-3-2%)</td>
<td>&gt;&gt;</td>
</tr>
</tbody>
</table>

0.5 1 2

Hypoxic modification better  Control better

---

**Meta Analysis - Hypoxic modification of radiotherapy in HNSCC**

* 95% CI.

** Numbers of patients Needed to Treat to achieve benefit in one patients.

---

Jens Overgaard. Radiother Oncol 2011; 100: 22-32
10/18 studies originated from Europe (misonidazole)
1219 ROG-HNCG: Study Design

Blinded & randomized trial; 640 patients (200 patients in the positive hypoxic gene profile)

**Step 1:** Potentially eligible patient with p16(-) confirmed, PIS/IC signature

**Step 2:** Lab tests, ...

**Step 3:**
- Sample for gene signature sent to central lab

**Trt plan for RT**

**CRT + nimorazole**
- Accl RT (70 Gy, 6 fx/wk) + cddp (40 mg/m² weekly x 5 or 100 mg/m² x 2) + nimorazole (1.2 g/m² daily)

**CRT + placebo**
- Accl RT (70 Gy, 6 fx/wk) + cddp (40 mg/m² weekly x 5 or 100 mg/m² x 2) + placebo
CA209-410/RTOG 3504: STUDY DESIGN\textsuperscript{1,2}

- Randomized phase III trial, with lead in, of cisplatin-based chemoradiotherapy ± nivolumab in patients with LA SCCHN

N=120

Key Eligibility Criteria
- Intermediate/high risk LA SCCHN
- ECOG PS ≤1
- p16 determination by immunohistochemistry
- No metastatic disease
- No prior radiotherapy of the tumor

Lead in

Phase III

- Study Start Date: June 2016
- Estimated Completion Date: N/A
- Estimated Primary Completion Date: March 2019
- Status: Not yet recruiting
- Sponsor: RTOG Foundation Inc

- Primary Outcome Measures:
  - Phase I: DLT
  - Phase III: OS

- Secondary Outcome Measures:
  - Phase I: None provided
  - Phase III: PFS, QoL

Abbreviations can be found in the speaker notes.
CCRT Standard Nonsurgical Therapy
What next in LA-SCCHN

- Should all patients be treated with concurrent CRT?
- Is further treatment intensification feasible and worth considering?
  - adding more cytotoxic chemotherapy (ICT)
  - adding targeted therapy
  - adding a hypoxic sensitizer to concurrent CRT
  - immunotherapy
- Can we select patients who might need less intensive therapy (de-escalation of locoregional therapy)?
A Role for ICT in HPV-positive OPC?

- No guidelines (NCCN)
- Proposed strategies
  A. The use of induction chemotherapy for patient selection
     - 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)\(^3\)
     - BRT with cetuximab (RTOG 1016; TROG 12.01, De-escal)

*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
Expectations for Systemic Therapy LA-SCCHN

- The best approach to larynx preservation (SALTORL)
- HD-CDDP 3-weekly vs LD-CDDP weekly (JCOG 1008)
- Treatment intensification in HPV(-) OPC, HPC and LC patients (CCRT vs CCRT +nimorazole; 1219 ROG-HNCG)
- De-intensification in HPV(+) OPC patients
  - CCRT vs Bioradiation with cetuximab (RTOG 1016, De-ESCALaTE study, TROG 12.01)
  - ICT to select patients for de-escalation (ECOG 1308)
- Studies in the elderly
- Integration of immunotherapy in primary therapy (RTOG 3504)
Standard Treatment Options in R/M-SCCHN 2016

• Resectable disease
  - Surgery at all times if possible
  - Postop RT or CCRT (if not complete) ¹

• Nonresectable disease
  - RT or CCRT (if no organ dysfunction/morbidity) ¹

• Recurrent/Metastatic disease
  - PF+cetuximab (in fit pts, performance status 0 or 1)²,³
  - Single drug therapy with MTX, taxane or cetuximab (PS2)³
  - Best supportive care only (PS3)²,³

## Completed Randomized Trials in First-Line Recurrent/Metastatic 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</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>Burtness et al</td>
<td></td>
<td>Cisplatin + placebo</td>
<td>10</td>
<td>2.7</td>
<td>8.0</td>
</tr>
<tr>
<td>J Clin Oncol 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXTREME</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>Vermorken et al</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</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>Vermorken et al</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>
<tr>
<td>Lancet Oncol 2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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
Overall Survival in EXTREME by p16 Status

**p16+ patients**

![Graph showing overall survival for p16+ patients with CT + cetuximab (n=18) compared to CT (n=23).]

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

**p16− patients**

![Graph showing overall survival for p16− patients with CT + cetuximab (n=178) compared to CT (n=162).]

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

Vermorken et al, Ann Oncol 2014

*HRs are CT + cetuximab vs CT; CI, confidence interval; HR, hazard ratio*
SPECTRUM: Overall Survival by p16 Status

**P16+ patients**

- **HR = 0.96 (95%CI: 0.59 - 1.57)**
- **p-value = 0.88**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS (95% CI) months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pmab + CT (n = 56)</td>
<td>10.9 (7.1 - 12.6)</td>
</tr>
<tr>
<td>CT alone (n = 37)</td>
<td>12.1 (7.6 - 17.4)</td>
</tr>
</tbody>
</table>

**P16- patients**

- **HR = 0.73 (95%CI: 0.57 - 0.94)**
- **p-value = 0.02**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS (95% CI) months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pmab + CT (n = 165)</td>
<td>11.8 (9.8 - 14.0)</td>
</tr>
<tr>
<td>CT alone (n = 153)</td>
<td>8.6 (6.9 - 11.3)</td>
</tr>
</tbody>
</table>

Quantitative interaction test p-value = 0.332
### Second-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>Stewart et al, 2009</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
Phase 3 CheckMate 141 Study Design

*Nivolumab in R/M SCCHN After Platinum Therapy*

Randomized, global, phase 3 trial of the efficacy and safety of nivolumab vs investigator's choice in patients with R/M SCCHN

**Key Eligibility Criteria**
- R/M SCCHN of the oral cavity, pharynx, or larynx
- Progression on or within 6 months of last dose of platinum-based therapy
- Irrespective of no. of prior lines of therapy
- Documentation of p16 to determine HPV status (oropharyngeal)
- Regardless of PD-L1 status

**Stratification factor**
- Prior cetuximab treatment

**Primary endpoint**
- OS

**Other endpoints**
- PFS
- ORR
- Safety
- DOR
- Biomarkers
- Quality of life

**Nivolumab**
- 3 mg/kg IV Q2W

**Investigator’s Choice**
- Methotrexate 40 mg/m² IV weekly
- Docetaxel 30 mg/m² IV weekly
- Cetuximab 400 mg/m² IV once, then 250 mg/m² weekly

*aTissue required for testing

DOR = duration of response; IV = intravenous; ORR = objective response rate; PFS = progression-free survival; Q2W = once every 2 weeks; R = randomized. Clinicaltrials.gov NCT02105636.

*Presented by Bob Ferris (ASCO 2016)*
Overall Survival
Nivolumab in R/M SCCHN After Platinum Therapy

<table>
<thead>
<tr>
<th></th>
<th>Median OS, mo (95% CI)</th>
<th>HR (97.73% CI)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Nivolumab (n = 240)</td>
<td>7.5 (5.5, 9.1)</td>
<td>0.70</td>
<td>0.0101</td>
</tr>
<tr>
<td>Investigator's Choice (n = 121)</td>
<td>5.1 (4.0, 6.0)</td>
<td>0.70</td>
<td>0.0101</td>
</tr>
</tbody>
</table>

1-year OS rate (95% CI)
36.0% (28.5, 43.4)

16.6% (8.6, 26.8)

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Investigator's Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>240</td>
<td>121</td>
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<tr>
<td>Months</td>
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<td>109</td>
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<td></td>
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</tr>
</tbody>
</table>

Courtesy of Bob Ferris (ASCO 2016)
Quality of Life and Symptom Burden

*Nivolumab in R/M SCCHN After Platinum Therapy*

- Nivolumab stabilized PROs while investigator’s choice led to meaningful declines in function and worsening of symptoms.

### EORTC QLQ-C30 Physical Function
- Week 9, 15, 21

### EORTC QLQ-C30 Social Function
- Week 9, 15, 21

### EORTC QLQ-H&N35 Absence of Sensory Problems
- Week 9, 15, 21

### EORTC QLQ-H&N35 Absence of Trouble With Social Contact
- Week 9, 15, 21
Expectations for Systemic Therapy
R/M-SCCHN

- Strategies to overcome resistance to cetuximab
- Development of anti-EGFR MoAb with stronger ADCC
- Testing other novel targeted agents in HPV(+/-) SCCHN
- Targeted agents directed by mutational status
- Studies with single agent checkpoint inhibitors (CPIs)
- Combination CPIs (or CPI + chemo) vs Extreme in 1st line
  - Keynote 048 (Pembro vs Pembro + chemo vs Extreme)
  - Kestrel (Durva vs Durva + Treme vs Extreme)
  - Checkmate 651 (Nivo + Ipi vs Extreme)
- Combinations of CPIs with targeted therapy in 1st line
Thank you
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
- Cisplatin: 448, 316, 217, 78
- Cisplatin+Cet: 447, 302, 197, 80

Ang KK et al, ASCO 2011 (abstract #5500)