Systemic Treatment in Squamous Cell Carcinoma of the Head and Neck (SCCHN)

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

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

- Lecturer fee from:
  Merck-Serono, Sanofi
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, targeted therapy, immunotherapy)

- **Communication / information / support / taking into account the wish of the patient**
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)**

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

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

### Standard options

<table>
<thead>
<tr>
<th>Option</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; Cisplatin dose: 100 mg/m² x3 during CF-RT

CCRT: 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)  Machtay M, et al. J Clin Oncol 2008; 26: 3582–3589
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)?
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.

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

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

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

Alternatives for high-dose 3-weekly cisplatin
- Other cisplatin dose or schedules
- Other cytotoxics (carboplatin, taxanes, low-dose gemcitabine)
- Biological agents (cetuximab, panitumumab, nimotuzumab)
- Hypoxic modification (nimorazole)

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
Weekly Low-Dose Versus Three-Weekly High-Dose Cisplatin for Concurrent Chemoradiation in Locoregionally Advanced Non-Nasopharyngeal Head and Neck Cancer: A Systematic Review and Meta-Analysis of Aggregate Data

Petr Szturz, Kristien Wouters, Naomi Kiyota, Makoto Tahara, Kumar Prabhash, Vanita Noronha, Ana Castro, Lisa Licitra, David Adelstein, Jan B. Vermorken

Figure 2. Overall survival analysis comparing weekly and three-weekly cisplatin given concurrently with postoperative radiotherapy.

Figure 3. Overall survival analysis comparing weekly and three-weekly cisplatin given concurrently with definitive radiotherapy.
Phase III randomized trial comparing weekly versus 3-weekly (W3W) cisplatin in patients receiving chemoradiation for locally advanced head and neck cancer

Vanita Noronha, MD DM
On behalf of Medical Oncology Department
Head and Neck Disease Management Group
Tata Memorial Hospital, Mumbai, India
Trial Design - W3W

ELIGIBILITY CRITERIA
- Age ≤ 70 yrs
- SCC of oral cavity/ pharynx/ larynx/ cervical lymphadenopathy of unknown primary
- Stage III / IV, no distant mets
- Adjuvant or definitive CRT
- If postop: high-risk features: ECE, close or + margins, T4 primary, > 2 LNs +
- No induction chemotherapy
- Adequate organ function

Stratify
- T-group (T0,1,2 vs T3,4)
- N-group (N0,1 vs N2,3)
- Therapy intent (adjuvant vs definitive)

Randomized 1:1 Open Label
n=150

3-weekly cisplatin
100mg/m²
D1,22,43 of RT

RT: 60 Gy/30 fr/6 wks (adj)
70 Gy/35 fr/7 weeks-(def)

n=150

Weekly cisplatin
30mg/m² with RT

Follow-up: Weekly during CRT, then Q3 mths x 2 yrs, then Q6 mths

Presented at: ASCO ANNUAL MEETING '17 | #ASCO17
Presented by: Vanita Noronha, Tata Mem Hosp

Presented By Vanita Noronha at 2017 ASCO Annual Meeting
Cumulative incidence curve for locoregional failure

2-yr LRR: Weekly 38.67% v/s 3-Weekly 24.67%

$p=0.014$

Gray's test; $HR=1.76$ (1.11-2.79)

Difference: 14%

(95% CI: 3.59-24.41)

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>150</th>
<th>75</th>
<th>45</th>
<th>24</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly Cisplatin</td>
<td>150</td>
<td>84</td>
<td>54</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>3 weekly Cisplatin</td>
<td>150</td>
<td>75</td>
<td>45</td>
<td>24</td>
<td>15</td>
</tr>
</tbody>
</table>
Overall survival

Median OS
weekly arm-39.5 mths vs
3-weekly arm-not reached,
HR-1.14 (95%CI, 0.79-1.65)

p = 0.48
Conclusions-W3W

- 3-weekly cisplatin is superior to weekly cisplatin in preventing locoregional relapses when combined with curative intent RT for locally advanced HNSCC.
- Increased severe acute toxicities.
Methods to Reduce the Toxicity of Cisplatin-based CCRT in SCCHN: Treatment Factors

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

New radiotherapy techniques
- IMRT and SW-IMRT
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- IMPT

Alternatives for high-dose 3-weekly cisplatin
- Other cisplatin dose or schedules
- Other cytotoxics (carboplatin, taxanes, low-dose gemcitabine)
- Biological agents (cetuximab, panitumumab, nimotuzumab)
- Hypoxic modification (nimorazole)
## 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 01216020</td>
<td>Italy</td>
<td>Cetuximab</td>
<td>Cisplatin</td>
<td>II (140)</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>
<tr>
<td>NCT 00496652</td>
<td>Denmark</td>
<td>Zalutumumab</td>
<td>Cisplatin</td>
<td>III (600)&lt;sup&gt;7&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); <sup>7</sup>6 fraction/week (RT ± Zalutumumab or CCRT ± zalutumumab)
## Chemoradiation vs 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 (2-yr OS)</th>
<th>RT+CET (2-yr OS)</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)
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)?
Induction Chemotherapy (ICT) in SCCHN 2017

• ICT does not have a clear established frontline role in the routine treatment of head and neck carcinomas of the major non-nasopharyngeal sites

• ICT→RT has an established role for organ preservation in advanced laryngeal and hypopharyngeal cancer

• ICT→cisplatin-based CCRT reduces distant metastases, but it does not increase OS and is more toxic than cisplatin-based CCRT alone.
Research Areas of Induction Chemotherapy for Treatment De-intensification

- ICT can be used as a tool to stratify patients by treatment response
- Applicable to good-prognosis HPV-associated OPC

Ongoing trials:
- OPTIMA HPV (NCT02258659)
- Quarterback trial (NCT01706939)*
- ECOG 1308 (NCT01084083)**

*Stage III and IV HPV OPC: 3x TPF, when CR/PR randomization between 56 Gy and 70 Gy, when NR standard CCRT
**Stage III-IVB resectable HPV OPC: 3x TCE, when CR-54Gy/27 fr, when PR/SD-69.3 Gy/33 fr

OPTIMA = Oro-Pharynx Tumor Induction Response
Stratified Therapy To Minimize Adverse Events

**Induction Chemotherapy**
- Low Risk
  - ≤T3 & ≤N2B & ≤10 PYH
  - N = 28
  - 1) Carboplatin AUC=6, d1
  - 2) Nab-paclitaxel 100 mg/m² d1/d18/d15

**Radiologic Assessment of Response**
- ≥ 50%
  - N = 20
  - pCR: 94.7%
  - Low-dose RT
    - PTV1: 50 Gy

- 30-50%
  - N = 6
  - pCR: 100%
  - Low-dose CRT
    - PTV1: 45 Gy
    - PTV2: 30 Gy

- < 30%
  - N = 2
  - Standard CRT
    - PTV1: 75 Gy
    - PTV2: 45 Gy

High Risk
- T4 or ≥N2C or >10 PYH

*The University of Chicago Medicine*
**OPTIMA = Oro-Pharynx Tumor Induction Response Stratified Therapy To Minimize Adverse Events**

### Induction Chemotherapy x 3 Cycles

1. Carboplatin AUC=6, d1
2. Nab-paclitaxel 100 mg/m² d1/d18/d15

### Radiologic Assessment of Response

- **≥ 50%**
  - Low-dose RT
    - PTV1: 50 Gy
    - N = 34
  - Low-dose CRT
    - PTV1: 45 Gy
    - PTV2: 30 Gy
    - N = 24

- **< 50%**
  - Standard CRT
    - PTV1: 75 Gy
    - PTV2: 45 Gy
    - N = 9

---

### Radiation Doses

- **Low-dose RT**
  - PTV1: 50 Gy

- **Low-dose CRT**
  - PTV1: 45 Gy
  - PTV2: 30 Gy

- **Standard CRT**
  - PTV1: 75 Gy
  - PTV2: 45 Gy
Results

**Overall Survival**

- 2-year OS: 100.0% (95% CI N/A)
- 2-year OS: 97.0% (95% CI 80.4% – 99.6%)

**Progression-Free Survival**

- 2-year PFS: 100.0% (95% CI N/A)
- 2-year PFS: 92.9% (95% CI 74.2% – 98.2%)
Results

**Locoregional Control**

- 2-year LRC: 100.0% (95% CI N/A)
- 2-year LRC: 95.8% (95% CI 73.9% – 99.4%)

**Distant Control**

- 2-year DC: 100.0% (95% CI N/A)
- 2-year DC: 100.0% (95% CI N/A)
G-tube Dependency

Time (months)

PEG-tube Dependent (%)

Low dose RT
Low dose CRT
Standard CRT

$P < .001$
# Ongoing Randomized Trials with Checkpoint Inhibitors in LA-SCCHN (≥100 pts)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>PembroRad</td>
<td>IIR (definitive)</td>
<td>Pembro+RT vs Cet +RT</td>
</tr>
<tr>
<td>PATHWay</td>
<td>IIR (adjuvant)</td>
<td>Pembro vs placebo</td>
</tr>
<tr>
<td>RTOG 3504</td>
<td>I/III (def.+adj)</td>
<td>Nivo+CRT (LD-P) vs Nivo+CRT (HD-P) vs Nivo+Cet+RT vs Nivo+RT</td>
</tr>
<tr>
<td>REACH</td>
<td>III (definitive)</td>
<td>P+RT vs Cet+Ave+RT* vs Cet+RT</td>
</tr>
<tr>
<td>KEYNOTE-412</td>
<td>III (definitive)</td>
<td>Pembro+P+RT vs Placebo+P+RT</td>
</tr>
<tr>
<td>JAVELIN HN-100</td>
<td>III (definitive)</td>
<td>Ave+P+RT vs Placebo+P+RT</td>
</tr>
</tbody>
</table>

Modified from Szturz and Vermorken, BMC Medicine 2017 (*separately in NPC and Oral cavity cancer)

Pembro=pembrolizumab (anti-PD1); Cet= cetuximab; P=cisplatin; RT=radiotherapy; CRT=chemoradiation
Nivo= nivolumab (anti-PD1); Ave= avelumab (anti-PD-L1)
Standard Treatment Options in R/M-SCCHN 2017

• 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) \(^2,^3\)

\(^3\)NCCN Guidelines
## 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
### 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 Stewart et al, 2009</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>ZALUTE Machiels et al, 2011</td>
<td>286</td>
<td>Z + BSC (-MTX)</td>
<td>6</td>
<td>2.3*</td>
<td>6.7°</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BSC (optional MTX)</td>
<td>1</td>
<td>1.9*</td>
<td>5.2°</td>
</tr>
<tr>
<td>LUX HN1 Machiels et al, 2015</td>
<td>483</td>
<td>Afatinib</td>
<td>10</td>
<td>2.6+</td>
<td>6.8</td>
</tr>
<tr>
<td></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;

*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), p=0.03
### Second-line Treatment with Targeting Drugs

#### Randomized 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>ECOG 1302 Argiris et al, 2013</td>
<td>270</td>
<td>D + Gefitinib</td>
<td>12</td>
<td>3.5 (TTP)</td>
<td>7.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D + placebo</td>
<td>6</td>
<td>2.1 (TTP)</td>
<td>6.0</td>
</tr>
<tr>
<td>BERIL-1 Trial Soulières et al, 2017</td>
<td>158</td>
<td>Buparlisib + paclitaxel</td>
<td>39</td>
<td>4.6*</td>
<td>10.4**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo + paclitaxel</td>
<td>14</td>
<td>3.5</td>
<td>6.5</td>
</tr>
<tr>
<td>CHECKMATE-141 Ferris et al, 2016</td>
<td>361</td>
<td>Nivolumab</td>
<td>13</td>
<td>2.0</td>
<td>7.5+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Investigator’s choice</td>
<td>6</td>
<td>2.3</td>
<td>5.1</td>
</tr>
</tbody>
</table>

*TTP = time to progression

*p=0.01 (one-sided); **p= 0.04 (one-sided); +p=0.01
## 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>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (n = 240)</td>
<td>7.5 (5.5, 9.1)</td>
<td>0.70 (0.51, 0.96)</td>
<td>0.0101</td>
</tr>
<tr>
<td>Investigator’s Choice (n = 121)</td>
<td>5.1 (4.0, 6.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 1-year OS rate (95% CI)

- **Nivolumab:** 36.0% (28.5, 43.4)
- **Investigator’s Choice:** 16.6% (8.6, 26.8)

### No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nivolumab</strong></td>
<td>240</td>
</tr>
<tr>
<td></td>
<td>167</td>
</tr>
<tr>
<td></td>
<td>109</td>
</tr>
<tr>
<td></td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>7</td>
</tr>
<tr>
<td><strong>Investigator’s Choice</strong></td>
<td>121</td>
</tr>
<tr>
<td></td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

*Courtesy of Bob Ferris (ASCO 2016)*
## Treatment-Related Adverse Events

### Nivolumab in R/M SCCHN After Platinum Therapy

<table>
<thead>
<tr>
<th>Event</th>
<th>Nivolumab (n = 236)</th>
<th>Investigator’s Choice (n = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade n (%)</td>
<td>Grade 3–4 n (%)</td>
</tr>
<tr>
<td>Any treatment-related AE in ≥ 10% of patients&lt;sup&gt;a&lt;/sup&gt;</td>
<td>139 (58.9)</td>
<td>31 (13.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33 (14.0)</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (8.5)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (6.8)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>12 (5.1)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>10 (4.2)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>3 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Treatment-related select AEs**

<table>
<thead>
<tr>
<th>Event</th>
<th>Nivolumab (n = 236)</th>
<th>Investigator’s Choice (n = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade n (%)</td>
<td>Grade 3–4 n (%)</td>
</tr>
<tr>
<td>Skin</td>
<td>37 (15.7)</td>
<td>0</td>
</tr>
<tr>
<td>Endocrine</td>
<td>18 (7.6)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>16 (6.8)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic</td>
<td>5 (2.1)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>5 (2.1)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Hypersensitivity/infusion reaction</td>
<td>3 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Renal</td>
<td>1 (0.4)</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>One Grade 5 event (hypercalcemia) in the nivolumab arm and one Grade 5 event (lung infection) in the investigator’s choice arm were reported. A second death occurred in the nivolumab arm subsequent to pneumonitis.

*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.
## Anti-PD-1/PD-L1 in Second-line R/M-SCCHN

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Second-line Chemother 1</th>
<th>Nivolumab Checkmate 141</th>
<th>Pembrolizumab 2</th>
<th>Durvalumab 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>5.8%</td>
<td>13.3%</td>
<td>18.0%</td>
<td>13.8%</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>0.8%</td>
<td>2.5%</td>
<td>2.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>5.0%</td>
<td>10.8%</td>
<td>16.0%</td>
<td>17.0%</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>2.3 months</td>
<td>2.0 months</td>
<td>2.1 months</td>
<td></td>
</tr>
<tr>
<td>6-month PFS</td>
<td>9.0%</td>
<td>19.7%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td><strong>Median OS</strong></td>
<td>5.1 months</td>
<td>7.5 months</td>
<td>8.0 months</td>
<td>8.5 months</td>
</tr>
<tr>
<td>6-months</td>
<td>16.6%</td>
<td>36.0%</td>
<td>38.0%</td>
<td>45%</td>
</tr>
</tbody>
</table>

1. From Checkmate 141 study (Ferris et al, NEJM 2016; DOI: 10.1056/NEJMoa1602252)
2. Seiwert et al, Lancet Oncol 2016 (online May 27, 2016)
3. Segal ESMO 2016 (abstract 9490)
Ongoing Randomized 2\textsuperscript{nd}-line Trials with Checkpoint Inhibitors in R/M-SCCHN as of April 2017 (≥100 pts)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>No</th>
<th>Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>CheckMate-141</td>
<td>III</td>
<td>361</td>
<td>Nivo vs SoC</td>
</tr>
<tr>
<td>CONDOR</td>
<td>IIR</td>
<td>240</td>
<td>Durva vs Treme vs Combination</td>
</tr>
<tr>
<td>KEYNOTE-040</td>
<td>III</td>
<td>466</td>
<td>Pembro vs SoC</td>
</tr>
<tr>
<td>EAGLE</td>
<td>III</td>
<td>720</td>
<td>Durva vs Durva+Treme vs SoC</td>
</tr>
<tr>
<td>KEYNOTE-122</td>
<td>IIR</td>
<td>160</td>
<td>Pembro vs SoC</td>
</tr>
</tbody>
</table>

Modified from Szturz and Vermorken, BMC Medicine, 2017

Nivo= nivolumab (anti-PD1); Durva= durvalumab (anti-PD-L1); Treme= tremelimumab (anti-CTLA-4)
Pembro= pembrolizumab (anti-PD1); SoC= standard of care
### Ongoing Randomized first-line Trials with Checkpoint Inhibitors in R/M-SCCHN (≥100 pts)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>No</th>
<th>Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>CheckMate-714</td>
<td>IIR</td>
<td>315</td>
<td>Nivo+Ipi vs Nivo+placebo</td>
</tr>
<tr>
<td>KESTREL</td>
<td>III</td>
<td>760</td>
<td>Durva vs Durva+Treme vs PFE</td>
</tr>
<tr>
<td>KEYNOTE-048</td>
<td>III</td>
<td>825</td>
<td>Pembro vs Pembro+PF vs PFE</td>
</tr>
<tr>
<td>CheckMate-651</td>
<td>III</td>
<td>490</td>
<td>Nivo+Ipi vs PFE</td>
</tr>
</tbody>
</table>

*Modified from Szturz and Vermorken, BMC Medicine, 2017*

Nivo= nivolumab (anti-PD1); Ipi= ipilimumab (anti-CTLA-4); Durva= durvalumab (anti-PD-L1); Treme= tremelimunab (anti-CTLA-4); Pembro= pembrolizumab (anti-PD1)
Systemic Therapy (CT/TT/IT) in R/M-SCCHN
Conclusions

- Still very poor prognosis (median OS 10 months)
- EXTREME first trial with improved outcome in first line
- Cetuximab only approved targeted agent in SCCHN
- Many unanswered questions related to anti-EGFR therapy:
  - Better partner than PF? / Role of maintenance therapy?
  - Can ADCC be enhanced? / A biomarker for response?
  - how to overcome resistance?
- Checkmate-141 first trial with improved outcome in 2nd line
- Both pembrolizumab and nivolumab approved
- Next steps: how to integrate IT in the SOC regimens?
THNO
6th Trends in Head and Neck Oncology
2-4 November 2017 Le Meridien Hotel, Nice, France
www.THNO2017.org