Chemoradiotherapy and Systemic Therapy 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, Synthon Biopharmaceuticals,

- Lecturer fee from:
  Merck-Serono, Sanofi, Bristol Myers Squibb
Outline of Presentation

• Important recent findings
• Multidisciplinary decision making
• Treatment strategies in LA-SCCHN
  - concurrent chemoradiotherapy (CCRT)
  - Bioradiotherapy (BRT) with cetuximab
  - Potential role of induction chemotherapy (ICT)
• Systemic therapy in R/M-SCCHN
• Conclusions
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)
- HNSCC is a highly immune-infiltrated cancer type
- Improved irradiation techniques available (IMRT)
- New imaging techniques available (PET)
- Quality of life of survivors is getting more attention
Multidisciplinary Team (MDT) Meetings

- Head and neck surgeon
- Radiation oncologist
- Medical oncologist
- Anesthesiologist, internist, general practitioner
- Radiologist
- Physical therapist, dietitian, social worker, psychologist a/o psychiatrist
- Biologist, pathologist
- Oncologic dentist
- Speech therapist
- Patient

Guidelines  Clinical trials

17th ESO-ESMO Masterclass Clinical Oncology
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**
What do Patients Look For? Prioritizing Treatment Outcomes

“Survival seems to be of paramount importance to both patient and non patient groups, overshadowing associated toxicities and potential dysfunction”

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
MACH-NC Meta-Analysis in Locoregionally Advanced SCCHN (*Practice changing*)

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Absolute benefit at 5 years</th>
<th>Risk reduction</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant</td>
<td>1 %</td>
<td>2 %</td>
<td>NS</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>2 %</td>
<td>5 %</td>
<td>NS</td>
</tr>
<tr>
<td>- NACT with PF</td>
<td>5 %</td>
<td>12%</td>
<td>0.01</td>
</tr>
<tr>
<td>Concurrent CRT</td>
<td>8 %</td>
<td>19%</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Pignon et al, Lancet 335:949, 2000  (Pooled data from trials performed between 1965 and 1993);
CRT= chemotherapy, mostly cisplatin 100 mg/m² x3 during radiotherapy
No concurrent regimen has been demonstrated to be superior to cisplatin alone during RT
Pignon et al. Radiother Oncol 2009; 92: 4-14
Updated MACH-NC Analysis (93 trials; 17,346 patients)
Radiother Oncol 2009; 92: 4-14*

*Pignon et al.
## Randomized Trials of Postoperative Chemoradiation *(Practice changing)*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment arms</th>
<th>No. pts</th>
<th>Median FUP</th>
<th>LR-CTR rate</th>
<th>Survival benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bachaud (1996)</td>
<td>RT / RT+CDDP</td>
<td>88</td>
<td>5 yrs</td>
<td>59% v 77% (p=0.08)</td>
<td>13% v 36 (p&lt;0.05)</td>
</tr>
<tr>
<td>Haffty (1997)</td>
<td>RT / RT+MMC</td>
<td>203</td>
<td>138 mo</td>
<td>54% v 76% (p=0.003)</td>
<td>42% v 48% (NS)</td>
</tr>
<tr>
<td>Bernier (2004)</td>
<td>RT / RT+CDDP</td>
<td>334</td>
<td>60 mo</td>
<td>(31% v 18%)* (p=0.007)</td>
<td>40% v 53%* (p=0.02)</td>
</tr>
<tr>
<td>Cooper (2004)</td>
<td>RT / RT+CDDP</td>
<td>459</td>
<td>46 mo</td>
<td>72% v 82% (p=0.01)</td>
<td>57% v 64%** (p=0.19)</td>
</tr>
</tbody>
</table>

* relapse rate  
* 5-year survival  
** 2-year survival (PFS at 2 yr: 45% v 54% [p=0.04])
Impact of CCRT According to Risk Factors

- Stage III-IV
- OP, OC with level 4 or 5 LN
- Perineural Disease
- Vascular Embolisms
- Margins + ECE
- 2+ pos. nodes

Bernier and Cooper, 2005
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)  Machtay M, et al. J Clin Oncol 2008; 26: 3582–3589
Study Design of Phase III Radiotherapy ± Cetuximab in Head and Neck Cancer

Locally advanced SCCHN stage III/IV, non-metastatic oropharynx, hypopharynx or larynx

N=424

RT + Cetuximab

Cet initial dose (400 mg/m²) Cet (250 mg/m²) + RT (wks 2–8)

Primary endpoint: Duration of locoregional control

Secondary endpoints: OS, PFS, RR, QoL, and safety


Cet, cetuximab; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RR, relative response; RT radiotherapy; SCCHN, squamous cell carcinoma of the head & neck
RT + Cetuximab Significantly Improves LRC and 5-year OS in LA-SCCHN

**LRC**

- **HR** = 0.68 [95% CI: 0.52–0.89]
- **p** = 0.005
- 3-year control rate = 47%
- 14.9 months

**OS**

- **HR** = 0.73 [95% CI: 0.56–0.95]
- **p** = 0.018
- 5-year survival rate = 46%
- 49.0 months


HR, hazard ratio; LA-SCCHN, locally advanced squamous cell carcinoma of the head & neck; LRC, locoregional control
Subset Analysis of the IMCL-9815 Trial

<table>
<thead>
<tr>
<th>Site of primary tumour</th>
<th>Radiotherapy alone</th>
<th>Radiotherapy plus cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Events</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>135</td>
<td>76</td>
</tr>
<tr>
<td>Larynx</td>
<td>51</td>
<td>32</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>27</td>
<td>22</td>
</tr>
<tr>
<td>Tumour stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AJCC T4</td>
<td>65</td>
<td>47</td>
</tr>
<tr>
<td>AJCC T1-3</td>
<td>148</td>
<td>83</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>122</td>
<td>66</td>
</tr>
<tr>
<td>Other</td>
<td>91</td>
<td>64</td>
</tr>
<tr>
<td>Radiotherapy fractionation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twice daily</td>
<td>37</td>
<td>20</td>
</tr>
<tr>
<td>Once daily</td>
<td>55</td>
<td>35</td>
</tr>
<tr>
<td>Concomitant boost</td>
<td>120</td>
<td>75</td>
</tr>
<tr>
<td>Overall stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AJCC IV</td>
<td>161</td>
<td>101</td>
</tr>
<tr>
<td>AJCC II-III</td>
<td>52</td>
<td>29</td>
</tr>
<tr>
<td>Nodal stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AJCC N1-3</td>
<td>175</td>
<td>109</td>
</tr>
<tr>
<td>AJCC N0</td>
<td>38</td>
<td>21</td>
</tr>
<tr>
<td>KPS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90-100</td>
<td>141</td>
<td>76</td>
</tr>
<tr>
<td>60-80</td>
<td>72</td>
<td>54</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>169</td>
<td>106</td>
</tr>
<tr>
<td>Female</td>
<td>44</td>
<td>34</td>
</tr>
<tr>
<td>EGFR-positive cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50%</td>
<td>81</td>
<td>50</td>
</tr>
<tr>
<td>≤50%</td>
<td>92</td>
<td>57</td>
</tr>
<tr>
<td>Unknown</td>
<td>40</td>
<td>23</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>65</td>
<td>43</td>
</tr>
<tr>
<td>&lt;65</td>
<td>148</td>
<td>87</td>
</tr>
</tbody>
</table>

Favours addition of cetuximab  Favours radiotherapy alone

*Bonner JA et al, Lancet Oncol 2010; 11: 21-28*
LRC in OPC Subpopulation According to p16 Status and Treatment Effect of RT + Cetuximab vs RT Alone

LRC interaction test p=NS

Rosenthal et al. ASCO 2014 (Abstract #6001); J Clin Oncol 2016; 34: 1300-1308
## Can Cetuximab Replace Cisplatin in CCRT?

**No large phase III comparison**

<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 (0.67-0.82)</strong>†</td>
<td>HR of death <strong>0.74 (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. <strong>High compliance. QoL BRT ~ RT†</strong></td>
</tr>
</tbody>
</table>

---

Thirty-one studies (4212 patients)
Overall cisplatin/RT faired better than cetuximab/RT (HR 0.32 [95% CI 0.09-0.55]), but survival outcomes were largely influenced by time of observation, being significantly different at 2 years, while the 3-year and 5-year and beyond time assessment showed no significant differences.

Subgroup analysis: in HPV-positive OPC, RT + cetuximab was superior in terms of OS, PFS and LRC.
# 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)¹</td>
</tr>
<tr>
<td>NCT 01874171</td>
<td>UK</td>
<td>Cetuximab</td>
<td>Cisplatin</td>
<td>III (304)²</td>
</tr>
<tr>
<td>NCT 01855451</td>
<td>Australia</td>
<td>Cetuximab</td>
<td>Cisplatin</td>
<td>III (200)³</td>
</tr>
<tr>
<td>NCT 00169247</td>
<td>France</td>
<td>Cetuximab</td>
<td>Cisplatin</td>
<td>II (156)⁴</td>
</tr>
<tr>
<td>NCT 00716391</td>
<td>Spain</td>
<td>Cetuximab</td>
<td>Cisplatin</td>
<td>III (458)⁵</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)⁶</td>
</tr>
<tr>
<td>NCT 00496652</td>
<td>Denmark</td>
<td>Zalutumumab</td>
<td>Cisplatin</td>
<td>III (600)⁷</td>
</tr>
</tbody>
</table>

¹ in HPV(p16)+OPC (RTOG-1016); ² De-Escalate study in HPV(p16)+OPC; ³ TROG 12.01 study in HPV(p16)+OPC; ⁴ Tremplin (after TPF); ⁵ after TPF; ⁶ AF (in exp. arm) vs SF (comparator); ⁷ 6 fraction/week (RT ± Zalutumumab or CCRT ± zalutumumab)
Facts on Induction Chemotherapy (ICT) 2018

- Optimal drug delivery: high response rates: transient toxicity\(^1\)
- Improves nutritional status and performance status
- Has established role in organ preservation strategies (LC, HPC)
- No compromise of subsequent RT or surgery\(^2\)
- Response to ICT predicts response to RT\(^3\)
- Decreases the occurrence of distant metastases
- Less effective (as CCRT) in locoregional disease control
- PF + taxane (TPF) most effective ICT regimen\(^4-6\)

\(^1\)Decker et al, Cancer 1983; \(^2\)First generation LP trials (Lefebvre et al, 2006); \(^3\)Ensley et al, Cancer 1984;
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)?
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.

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>
</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>

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

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

**Low Risk**
- ≤T3 & ≤N2B & ≤10 PYH

**High Risk**
- T4 or ≥N2C or >10 PYH

**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
- 30-50%
  - Low-dose CRT
    - PTV1: 45 Gy
    - PTV2: 30 Gy
- < 30%
  - Standard CRT
    - PTV1: 75 Gy
    - PTV2: 45 Gy

Seiwert et al. MHNCS 2018
OPTIMA = Oro-Pharynx Tumor Induction Response Stratified Therapy To Minimize Adverse Events

Low Risk

\[ \leq T3 \text{ & } \leq N2B \text{ & } 10 \text{ PYH} \]

Induction Chemotherapy x 3 Cycles

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

Radiologic Assessment of Response

\[ \geq 50\% \]

Low-dose RT
PTV1: 50

\[ \leq T3 \text{ & } \leq N2B \text{ & } 10 \text{ PYH} \]

High Risk

\[ T4 \text{ or } \geq N2C \text{ or } >10 \text{ PYH} \]

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

< 50\%

Standard CRT
PTV1: 75 Gy
PTV2: 45 Gy

Seiwer et al. MHNCS 2018
### Results: CONSORT

<table>
<thead>
<tr>
<th>Enrolled on Protocol ( (N = 62) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk ( (N = 28) )</td>
</tr>
<tr>
<td>Initiated IC ( (N = 28) )</td>
</tr>
<tr>
<td>Completed IC ( (N = 28) )</td>
</tr>
<tr>
<td>≥50% Response → RT50 ( (N = 20) )</td>
</tr>
<tr>
<td>30-50% Response → CRT45 ( (N = 6) )</td>
</tr>
<tr>
<td>&lt;30% Response → CRT75 ( (N = 2) )</td>
</tr>
<tr>
<td>Initiated RT/CRT ( (N = 28) )</td>
</tr>
<tr>
<td>Completed RT/CRT ( (N = 28) )</td>
</tr>
</tbody>
</table>

| High Risk \( (N = 34) \)          |
| Initiated IC \( (N = 34) \)       |
| Transferred Care \( (N = 1) \)    |
| Completed IC \( (N = 33) \)       |
| ≥50% Response → CRT45 \( (N = 24) \) |
| <50% Response → CRT75 \( (N = 9) \) |
| Initiated CRT \( (N = 33) \)      |
| Died during CRT \( (N = 1) \)     |
| Completed CRT \( (N = 32) \)      |

Seiwert et al. MHNCS 2018
Results

- **Post-Treatment Biopsy/ND:**
  - Mean 7.3 weeks after RT/CRT (IQR 5.9-8.4)
  - Mean 26 nodes removed (IQR 18-33)

- **Pathologic CR Rates: 91.5%**
  - Low-dose RT: 94.7% (18/19)
  - Low-dose CRT (CRT): 89.3% (25/28)
    - *Low risk pts: 100% (6/6)*
    - *High risk pts: 86.4% (19/22)*
**Overall Survival**

- 2-year OS: 100%
- 2.5-year OS: 85.7%
- 2-year PFS: 91.0%
- 2.5-year PFS: 91.0%

**Progression-Free Survival**

- 2-year PFS: 93.8%
- 2.5-year PFS: 93.8%
- 2-year OS: 97.0%
- 2.5-year OS: 97.0%

**Locoregional Control**

- 2-year LRC: 100%
- 2.5-year LRC: 100%
- 2-year DC: 91.0%
- 2.5-year DC: 91.0%

**Distant Control**

- 2-year DC: 96.8%
- 2.5-year DC: 96.8%
### Acute Toxicity (%)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Grade ≥3 Mucositis</th>
<th>P-Value</th>
<th>Grade ≥3 Dermatitis</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose RT</td>
<td>15.0</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Low dose CRT</td>
<td>46.7</td>
<td>0.01</td>
<td>10.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Standard CRT</td>
<td>63.6</td>
<td></td>
<td>45.5</td>
<td></td>
</tr>
</tbody>
</table>

### G-tube dependency

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>PEG-Dependency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 Mos.</td>
</tr>
<tr>
<td>Low dose RT</td>
<td>0</td>
</tr>
<tr>
<td>Low dose CRT</td>
<td>6.9</td>
</tr>
<tr>
<td>Standard CRT</td>
<td>18.2</td>
</tr>
</tbody>
</table>

*Seiwert et al. MHNCS 2018*
Standard Treatment Options in R/M-SCCHN 2018

- 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
  - First-line: EXTREME (platinum/5-FU/cetuximab) \(^2,3\)
  - Alternatives in unfavorable pts: single agents ± cetuximab
  - Second-line: CheckMate-141 (nivolumab single agent) \(^3\)
  - Pembrolizumab also approved for same indication \(^3\)
  - Best supportive care only (PS3) \(^2,3\)

Systemic Therapy Options are Evolving for SCCHN

Evolution of systemic therapy

1960s: 5-FU, methotrexate
1970s: Cisplatin
1990s–2000s: Taxanes
2000s: EGFR inhibitors

IMMUNOTHERAPY


Courtesy of Ethan Argiris
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Regimen</th>
<th>ORR (%)</th>
<th>Median OS (months)</th>
<th>Significant OS benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobs et al</td>
<td>249</td>
<td>Cisplatin + 5-FU</td>
<td>32*</td>
<td>5.5</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin</td>
<td>17</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-FU</td>
<td>13</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>Forastiere et</td>
<td>277</td>
<td>Cisplatin + 5-FU</td>
<td>32*</td>
<td>6.6</td>
<td>No</td>
</tr>
<tr>
<td>al 1992</td>
<td></td>
<td>Carboplatin + 5-FU</td>
<td>21</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methotrexate</td>
<td>10</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Clavel et al</td>
<td>382</td>
<td>CABO</td>
<td>34*</td>
<td>7.3</td>
<td>No</td>
</tr>
<tr>
<td>1994</td>
<td></td>
<td>Cisplatin + 5-FU</td>
<td>31*</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin</td>
<td>15</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>Gibson et al</td>
<td>218</td>
<td>Cisplatin + 5-FU</td>
<td>27</td>
<td>8.7</td>
<td>No</td>
</tr>
<tr>
<td>2005</td>
<td></td>
<td>Cisplatin + paclitaxel</td>
<td>26</td>
<td>8.1</td>
<td></td>
</tr>
<tr>
<td>Urba et al</td>
<td>795</td>
<td>Cisplatin/Pemetrexed</td>
<td>12</td>
<td>7.3</td>
<td>No</td>
</tr>
<tr>
<td>2012</td>
<td></td>
<td>Cisplatin/placebo</td>
<td>8</td>
<td>6.3</td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant

# First-line Treatment with Targeted Therapies

Randomized 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>EXTREME</td>
<td>442</td>
<td>PF$^1$ + cetuximab PF$^1$</td>
<td>36$^a$</td>
<td>5.6$^b$</td>
<td>10.1$^c$</td>
</tr>
<tr>
<td>Vermorken et al</td>
<td></td>
<td></td>
<td>20</td>
<td>3.3</td>
<td>7.4</td>
</tr>
<tr>
<td>SPECTRUM</td>
<td>657</td>
<td>PF$^2$ + panitumumab PF$^2$</td>
<td>36$^a$</td>
<td>5.8$^b$</td>
<td>11.1</td>
</tr>
<tr>
<td>Vermorken et al</td>
<td></td>
<td></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>
<tr>
<td>ECOG-ACRIN</td>
<td>403</td>
<td>4 Pt doublets$^3$ + bev 4 Pt doublets$^3$</td>
<td>36$^a$</td>
<td>6.1$^b$</td>
<td>12.6</td>
</tr>
<tr>
<td>Argiris et al</td>
<td></td>
<td></td>
<td>25</td>
<td>4.4</td>
<td>11.0</td>
</tr>
<tr>
<td>ASCO 2017</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PF$^1$ = cisplatin or carboplatin plus 5-FU; PF$^2$ = cisplatin plus 5-FU, PT$^3$ = cisplatin or carboplatin plus docetaxel

$^a$, $^b$, $^c$: significant differences

$^3$PF or PT both with or without bevacizumab
EXTREME: Toxicity of PFE vs PF

Grade 3 and 4 AEs with a frequency ≥5%† in either arm of the safety population

- Anemia
- Neutropenia
- Thrombocytopenia
- Leukopenia
- Hypokalemia
- Hypomagnesemia
- Febrile neutropenia
- Anorexia
- Cardiac events
- Vomiting
- Asthenia
- Dyspnea
- Sepsis
- Skin reactions
- Infusion reaction

*Platinum-based CT, consisting of cisplatin/carboplatin + 5-FU;
‡p=0.05 vs CT alone; †p=0.02 vs CT alone; ‡p<0.001 vs CT alone
AE, adverse event

EXTREME: Overall Survival by p16 Status

**p16+ patients**

- Median OS: 12.6 vs 9.6
- HR (95% CI): 0.63 (0.30–1.34)
- p-value: 0.224

**p16− patients**

- Median OS: 9.7 vs 7.3
- HR (95% CI): 0.82 (0.65–1.04)
- p-value: 0.106

*HRs are CT + cetuximab vs CT. Cl, confidence interval; HR, hazard ratio.*
EXTREME – Overall Survival
Long-term follow-up

Vermorken et al. ASCO 2014 (abstr. #6021)
<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><strong>IMEX</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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><strong>ZALUTE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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><strong>ECOG 1302</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></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><strong>LUX HN1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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*
Immunologic Approaches in SCCHN

• Immunomodulators have shown ability to enhance the ADCC of cetuximab and to potentiate the effect of CT

• Adoptive cell therapy

• Therapeutic vaccines

• Cytotoxic T-lymphocyte-associated protein 4 check-point inhibitors may activate T-cell activation

• Pairing PD-1 and PD-L1 allows cancers to evade the host immune system. PD-1/PD-L1 blockage leads to T-cell-based immune responses.
**Immune Checkpoint Inhibitors (ICIs) Under Development for R/M-SCCHN**

1. **Nivolumab**
   - IgG4
   - Fully human
   - High Affinity for PD-1 (KD ~ 2.6 nM)

2. **Pembrolizumab**
   - IgG4
   - Humanized
   - High Affinity for PD-1 (KD ~ 29 pM)

3. **Other PD-1/PD-L1 agents in development:**
   - PD-L1 agents – Atezolizumab (IgG1), Durvalumab (IgG1), Avelumab (IgG1)

4. **CTLA-4 agents:**
   - Ipilimumab (IgG1), Tremelimumab (IgG2)

*Courtesy from Seiwert (modified)*
Phase III CheckMate 141: Study Design
Nivolumab in R/M SCCHN After Platinum Therapy

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 number of prior lines of therapy
- Documentation of p16 to determine HPV status (oropharyngeal)
- Regardless of PD-L1 status

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

Nivolumab
3 mg/kg IV q 2 w

Primary endpoint
- OS

Other endpoints
- PFS
- ORR
- Safety
- DoR
- Biomarkers
- QoL

Stratification factor
- Prior cetuximab treatment

DoR, duration of response; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; q 2 w, once every 2 weeks; R/M, recurrent or metastatic

**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</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 (0.51, 0.96)</td>
<td>0.0101</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)

*Courtesy of Bob Ferris (ASCO 2016)*
CheckMate 141: Overall Survival by Tumor PD-L1 Expression
Nivolumab in R/M SCCHN After Platinum Therapy

PD-L1 ≥1%

- HR (95% CI)
  - 0.55 (0.36, 0.83)

PD-L1 <1%

- HR (95% CI)
  - 0.89 (0.54, 1.45)

CheckMate 141: Overall Survival by p16 Status
Nivolumab in R/M SCCHN After Platinum Therapy

P16-Positive

HR (95% CI) 0.56 (0.32, 0.99)

No. at Risk
Nivolumab 63 49 35 18 10 3 0
Investigator's Choice 29 20 11 4 1 0 0

Months
Overall Survival, % of Patients

P16-Negative

HR (95% CI) 0.73 (0.42, 1.25)

No. at Risk
Nivolumab 50 32 25 12 6 1 0
Investigator's Choice 36 26 13 7 3 1 0

Months
Overall Survival, % of Patients

# CheckMate141: 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>Any treatment-related AE in ≥10% of patients</td>
<td>139 (58.9)</td>
<td>86 (77.5)</td>
</tr>
<tr>
<td>Any treatment-related AE in ≥10% of patients</td>
<td>31 (13.1)</td>
<td>39 (35.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33 (14.0)</td>
<td>19 (17.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (8.5)</td>
<td>23 (20.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (6.8)</td>
<td>15 (13.5)</td>
</tr>
<tr>
<td>Anemia</td>
<td>12 (5.1)</td>
<td>18 (16.2)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>10 (4.2)</td>
<td>16 (14.4)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>3 (1.3)</td>
<td>14 (12.6)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>14 (12.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment-related select AEs</th>
<th>Nivolumab</th>
<th>Investigator’s Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>37 (15.7)</td>
<td>14 (12.6)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>18 (7.6)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>16 (6.8)</td>
<td>16 (14.4)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>5 (2.1)</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>5 (2.1)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Hypersensitivity/infusion reaction</td>
<td>3 (1.3)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Renal</td>
<td>1 (0.4)</td>
<td>2 (1.8)</td>
</tr>
</tbody>
</table>

*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. AE, adverse event.

Nivolumab-treated patients experienced stable PROs
Investigator’s choice–treated patients had statistically significant and clinically meaningful worsening of symptoms compared with nivolumab

EORTC QLQ-H&N35 Symptom Burden
Nivolumab in R/M SCCHN After Platinum Therapy

• Nivolumab-treated patients experienced stable PROs
• Investigator’s choice–treated patients had statistically significant and clinically meaningful worsening of symptoms compared with nivolumab

EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Module; PRO, patient reported outcomes
CheckMate 141: Outcomes in the First-line R/M-SCCHN

**Figure 2.** OS among patients receiving 1L R/M nivolumab or IC after platinum-based therapy in the primary/adjunct setting.

- **ORR:** 19.2% vs 11.5%

<table>
<thead>
<tr>
<th></th>
<th>Median OS, mo (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivo (n = 52)</td>
<td>7.7 (3.1, 13.8)</td>
<td>0.56</td>
</tr>
<tr>
<td>IC (n = 26)</td>
<td>3.3 (2.1, 6.4)</td>
<td>(0.33, 0.95)</td>
</tr>
</tbody>
</table>

Gillison et al. ASCO 2017
Gillison et al. The Oncologist 2018
Hyperprogression during anti-PD-1/PD-L1 therapy in patients with recurrent and/or metastatic head and neck squamous cell carcinoma

E. Saâda-Bouzid¹, C. Defauscheux², A. Karabajakian³, V. P. Coloma⁴, V. Servois⁵, X. Paoletti⁶, C. Even⁴, J. Fayette³, J. Guigay⁷, D. Loirat², F. Peyrade⁷, M. Alt³, J. Gal⁷ & C. Le Tourneau⁷,⁸

Hyperprogressive Disease Is a New Pattern of Progression in Cancer Patients Treated by Anti-PD-1/PD-L1

Stéphane Champiat¹,², Laurent Dercle³, Samy Ammari⁴, Christophe Massard¹, Antoine Hollebecque¹, Sophie Postel-Vinay¹,², Nathalie Chaput⁵,⁶,⁷,⁸, Alexander Eggermont⁹, Aurélien Marabelle¹,¹⁰, Jean-Charles Soria¹,², and Charles Feré¹,¹¹,¹²
Take-Home Messages

- Multidisciplinary Team meetings are key
- Treatment in LA-SCCHN should focus at LRC
- Cisplatin-based CCRT is SoC; no other TRT outperforms
- HPV-positive OPC separate entity, but treatment the same
- ICT: new opportunities on the horizon

- EXTREME regimen (PFE) is SoC in 1st-line R/M-SCCHN
- Immune CPIs have shown OS benefit in 2nd-line
- Continuum of care possible (but cave hyperprogression)
Thank you