Update on the Management of Squamous Cell Carcinoma of the Head and Neck

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

6th ESO-ESMO-EEBR-Masterclass in Medical Oncology, Split, Croatia, April 12-17, 2019
Conflict of Interest Disclosure (2019)

- Participated in Advisory Boards of:
  AstraZeneca, Boehringer Ingelheim, Debiopharm Innate Pharma, Merck Serono, Merck Sharp & Dome Corp, PCI Biotech, Synthon Biopharmaceuticals, WntResearch

- Lecturer fee from:
  MSD, Merck-Serono, Sanofi, and BMS
Head and Neck Cancer (HNC)
A changing population

- Worldwide HNC is still increasing (>800,000 in 2016)
- Majority still tobacco and alcohol related
- Increase of viral-associated OPC, less so in elderly\(^1\)
- SEER data: 47% of SCCHN patients >65 years of age
- The incidence of HNC among older patients is expected to increase
  34% over the next 10 years, and 64% over the next 20 years\(^2\).
- Most studies use the age of 70 (or even 75) as a cut-off for being old

# Head and Neck Cancer (HNC)

## A changing disease

<table>
<thead>
<tr>
<th></th>
<th>HPV-pos</th>
<th>HPV-neg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anatomical</strong></td>
<td>Tonsil, base of tongue</td>
<td>All sites</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Non-keratinized</td>
<td>Keratinized</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Younger cohorts</td>
<td>Olders cohorts</td>
</tr>
<tr>
<td><strong>Sex ratio</strong></td>
<td>3:1 men</td>
<td>3:1 men</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td>Tx, T1-2</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td>Sexual behaviour</td>
<td>Alcohol, tobacco</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>Increasing</td>
<td>Decreasing</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td>Improved</td>
<td>Unchanging</td>
</tr>
</tbody>
</table>

Marur et al, 2010
Head and Neck Cancer (HNC)
A changing treatment

- Surgery
  - reconstructive surgery
  - organ sparing techniques
  - TO(R)S

- Radiotherapy
  - altered fractionation schedules
  - Better targeting (CT-MRI, PET, IGRT)
  - New RT techniques (IMRT, STRT, PT)
  - Combined approached: CT, TT, hypoxic cell modifiers

- Systemic therapy
  - New cytotoxic agents
  - Molecular targeted therapies
  - Immunotherapy
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

ESO-ESMO EEBR Masterclass 2019
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 Algorithm for the Management of Head and Neck Cancer

**Curative Intent**
Non-metastatic (I-IVB)*

**Early stage (I/II)**
- Single modality
  - Surgery preferred in OC, PNS
  - Robotic surgery emerging role in OPC
  - RT preferred in OPC, NPC and HPC
  - Surgery/RT in glottic cancer

**Advanced stage (III/IVA/IVB)**
- Multimodality
  - OC, PNS: PORT ± CT
  - OPC, NPC: CCRT ± SS
  - L, HP: CCRT or ICT → RT/CCRT for LP
  - BRT with cetuximab

**Palliative Intent**
Metastatic (IVC) or unable to tolerate standard treatment

**Metastatic with good PS**
- LT first → ST
  - ST first → LT
- CT ± TT
- Immunotherapy
  - Treat Oligomets aggressively?

**Very frail**
poor PS
unable to tolerate treatment
- BSC

**OC**: oral cavity; **PNS**: paranasal sinus; **OPC**: oropharynx cancer; **NPC**: nasopharynx cancer; **HPC**: hypopharynx cancer; **PORT**: postoperative radiotherapy; **CT**: chemotherapy; **CCRT**: concurrent chemoradiation; **SS**: salvage surgery; **ICT**: induction chemotherapy; **LP**: larynx preservation; **BRT**: bioradiotherapy; **LT**: local treatment; **ST**: systemic treatment; **TT**: targeted therapy; **RT**: radiotherapy; **PS**: performance status

UICC Manual of Clinical Oncology, Ninth edition, Published 2015 (modified)
*except for those unable to tolerate standard therapy due to co-morbidity or poor PS
EBM for Treatment in Early Stage SCCHN

Selection treatment modality (ERT vs BT vs S) based on:

• Primary tumor site
• Age
• Comorbidity
• Occupation, preference and compliance
• Quality of life following the treatment
• Availability of expertise in RT or surgery
• History of a previous malignant lesion in the H&N

Corvò R, 2007 (ERT=external radiotherapy, BT=brachytherapy, S=surgery)
Treatment Algorithm for the Management of Head and Neck Cancer

Curative Intent
Non-metastatic (I-IVB)*

Early stage (I/II)
Single modality
• Surgery preferred in OC, PNS
• Robotic surgery emerging role in OPC
• RT preferred in OPC, NPC and HPC
• Surgery/RT in glottic cancer

Advanced stage (III/IVA/IVB) Multimodality
• OC, PNS: PORT ± CT
• OPC, NPC: CCRT ± SS
• L, HP: CCRT or ICT → RT/CCRT for LP
• BRT with cetuximab

Palliative Intent
Metastatic (IVC) or unable to tolerate standard treatment

Metastatic with good PS
• LT first → ST
ST first → LT
• CT ± TT
• Immunotherapy
• Treat Oligomets aggressively?

Very frail
poor PS unable to tolerate treatment
• BSC

OC: oral cavity; PNS: paranasal sinus; OPC: oropharynx cancer; NPC: nasopharynx cancer; HPC: hypopharynx cancer; PORT; postoperative radiotherapy; CT; chemotherapy; CCRT: concurrent chemoradiation; SS: salvage surgery; ICT: induction chemotherapy; LP: larynx preservation; BRT: bioradiotherapy; LT: local treatment; ST: systemic treatment; TT: targeted therapy; RT: radiotherapy; PS: performance status
UICC Manual of Clinical Oncology, Ninth edition, Published 2015 (modified)
* except for those unable to tolerate standard therapy due to co-morbidity or poor PS
<table>
<thead>
<tr>
<th>Standard options</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**

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
High-Dose Cisplatin/RT Preferred Approach for LA-SCCHN in Guidelines

Should all patients be treated with high-dose cisplatin concomitantly with radiotherapy?
Current Standard, High-dose Cisplatin
Three-Step Recommendation*

• Absolute contra-indications to cisplatin¹
  - Both high- and low-dose regimens excluded
  - Carboplatin/5-FU schedule (GORTEC)²
  - Cetuximab³, docetaxel/cetuximab
  - Radiotherapy alone

• Relative contra-indications to cisplatin¹ (grey zone)
  - Lowering the cisplatin peak concentration
  - see alternative options under absolute contra-indications

• No contra-indications
  - HD-Cis during conventional or altered fractionation RT

* Szturz et al, Frontiers in Oncol, 2018 submitted
Groups of Special Interest

- Patients with HPV-associated oropharyngeal squamous cell carcinoma (OPSCC), who may expect a long life
- Patients with comorbidities for whom full dose treatment might be difficult to tolerate
- Elderly patients
  - in the primary disease setting
  - in the recurrent/metastatic disease setting
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.

Comorbidity and Survival

Overgaard et al. DAHANCA Database. Clinical Epidemiology 2016; 8: 491-496
Impact of Charlson Comorbidity Index on outcome–specific HNC comorbidity index used in daily practice
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
Once-a-Week Versus Once-Every-3-weeks Cisplatin Chemoradiation for Locally Advanced Head and Neck Cancer: A Phase III Randomized Noninferiority Trial

## Cisplatin versus Cetuximab with Definitive Concurrent Radiotherapy for HNSCC: An Analysis of Veteran’s Health Data

<table>
<thead>
<tr>
<th></th>
<th>Median OS (yrs)</th>
<th>CET</th>
<th>CIS</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted</strong></td>
<td></td>
<td>1.5</td>
<td>3.8</td>
<td>1.78</td>
<td>1.63-1.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>PS matched</strong></td>
<td></td>
<td>1.8</td>
<td>4.2</td>
<td>1.66</td>
<td>1.48-1.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oral cavity (n=135)</td>
<td></td>
<td>0.8</td>
<td>1.0</td>
<td>1.62</td>
<td>1.07-2.44</td>
<td>0.02</td>
</tr>
<tr>
<td>Oropharynx (n=1.485)</td>
<td></td>
<td>1.0</td>
<td>4.6</td>
<td>1.63</td>
<td>1.42-1.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Larynx/HypoPh (n=477)</td>
<td></td>
<td>1.4</td>
<td>3.2</td>
<td>1.87</td>
<td>1.49-2.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low dose Cis, PS (n=902)</td>
<td></td>
<td>1.6</td>
<td>3.9</td>
<td>1.53</td>
<td>1.30-1.80</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Bauml J, et al. ASCO 2018; abstract #6073

*PS matched
Radiotherapy plus Cetuximab or Cisplatin in HPV-Positive Oropharyngeal Cancer

NRG Oncology RTOG1016

Interpretation

For patients with HPV-positive oropharyngeal carcinoma, radiotherapy plus cetuximab showed inferior overall survival and progression-free survival compared with radiotherapy plus cisplatin. Radiotherapy plus cisplatin is the standard of care for eligible patients with HPV-positive oropharyngeal carcinoma.

Gillison et al. Lancet Oncol. Published online November 15, 2018, [http://dx.doi.org/10.1016/S0140-6736(18)32779-x](http://dx.doi.org/10.1016/S0140-6736(18)32779-x)
Radiotherapy plus Cisplatin or Cetuximab in Low-risk HPV-positive Oropharyngeal Cancer
De-ESCALaTE HPV

Interpretation: Compared with the standard cisplatin regimen, cetuximab showed no benefit in terms of reduced toxicity, but instead showed significant detriment in terms of tumour control. Cisplatin and radiotherapy should be used as the standard of care for HPV-positive low-risk patients who are able to tolerate cisplatin.

Mehanna et al. Lancet Oncol. Published Online November 15, 2018, http://dx.doi.org/10.1016/S0140-6736(18)32752-1
### Treatment Algorithm for the Management of Head and Neck Cancer

#### Curative Intent
- **Non-metastatic (I-IVB)**

#### Early stage (I/II)
- **Single modality**
  - Surgery preferred in OC, PNS
  - Robotic surgery emerging role in OPC
  - RT preferred in OPC, NPC and HPC
  - Surgery/RT in glottic cancer

#### Advanced stage (III/IVA/IVB)
- **Multimodality**
  - OC, PNS: PORT ± CT
  - OPC, NPC: CCRT ± SS
  - L, HP: CCRT or ICT → RT/CCRT for LP
  - BRT with cetuximab

#### Palliative Intent
- **Metastatic (IVC) or unable to tolerate standard treatment**

#### Metastatic with good PS
- LT first → ST
- ST first → LT
- CT ± TT
- Immunotherapy
- Treat Oligomets aggressively?

#### Very frail
- Poor PS unable to tolerate treatment
- BSC

---

OC: oral cavity; PNS: paranasal sinus; OPC: oropharynx cancer; NPC: nasopharynx cancer; HPC: hypopharynx cancer; PORT; postoperative radiotherapy; CT; chemotherapy; CCRT: concurrent chemoradiation; SS: salvage surgery; ICT: induction chemotherapy; LP: larynx preservation; BRT: bioradiotherapy; LT: local treatment; ST: systemic treatment; TT: targeted therapy; RT: radiotherapy; PS: performance status

*except for those unable to tolerate standard therapy due to co-morbidity or poor PS*
Relapsing SCCHN: Heterogenous Group

- **Type of relapse:**
  - local a/o regional only; metastatic only; both
- **Type of primary therapy**
  - single modality (S or RT)
  - combined modality (S→LT*, CCRT, BRT, ICT→LT*)
- **Interval “primary TRT-Relapse”:**
  - short interval (<6 months) after CCRT → poor prognosis
- **Influence of HPV status**:  
  - better OS in patients with p16+ oropharyngeal carcinoma

*LT= local therapy, i.e. RT, CCRT or BRT; S= surgery; RT= radiotherapy; CCRT= concurrent chemoradiation; BRT= RT + cetuximab; ICT= induction chemotherapy; **Fakhry et al. J Clin Oncol 32 10.1200/JCO.2014.55.193
# Development of Chemotherapy in R/M SCCHN

1977: cisplatin shows efficacy in 1\textsuperscript{st}-line SCCHN

<table>
<thead>
<tr>
<th>Regimen</th>
<th>ORR (%)</th>
<th>Median OS (months)</th>
<th>Significant OS benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>16</td>
<td>5.0</td>
<td>No</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>8</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Forastiere et al 1992</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin + 5-FU</td>
<td>32*</td>
<td>6.6</td>
<td>No</td>
</tr>
<tr>
<td>Carboplatin + 5-FU</td>
<td>21</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>10</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Clavel et al 1994</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABO</td>
<td>34*</td>
<td>7.3</td>
<td>No</td>
</tr>
<tr>
<td>Cisplatin + 5-FU</td>
<td>31*</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>15</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>Gibson et al 2005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin + 5-FU</td>
<td>27</td>
<td>8.7</td>
<td>No</td>
</tr>
<tr>
<td>Cisplatin + paclitaxel</td>
<td>26</td>
<td>8.1</td>
<td></td>
</tr>
<tr>
<td>Vermorken et al 2008</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platinum + 5-FU</td>
<td>20</td>
<td>7.4</td>
<td>Yes</td>
</tr>
<tr>
<td>Platinum + 5-FU + Cetuximab</td>
<td>36*</td>
<td>10.1*</td>
<td></td>
</tr>
</tbody>
</table>

CABO, cisplatin, methotrexate, bleomycin, vincristine

*significant

EXTREME: A Breakthrough in First-line R/M-SCCHN

Overall survival (%)

- Cetuximab + chemotherapy* (n=222)
- Chemotherapy* (n=220)

HR 0.80 (95% CI 0.64–0.99)
p=0.04

+2.7 months

Maximize OS/PFS
Improve response rate
Control symptoms
Manage side effects
Maintain QoL

*Chemotherapy consisted of cisplatin/carboplatin + 5-FU
CheckMate141 & KEYNOTE012: A Breakthrough in Second-line R/M-SCCHN

<table>
<thead>
<tr>
<th>Study/author</th>
<th>Agent</th>
<th>Design</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>CheckMate 141</td>
<td>Nivolumab (3 mg/kg q 2w)</td>
<td>Phase III randomized</td>
<td>progressive disease &lt;6 mo of platinum</td>
</tr>
<tr>
<td>Ferris et al(^1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keynote-012</td>
<td>Pembrolizumab (10 mg/kg q 2w)</td>
<td>Phase Ib single arm</td>
<td>PD-L1 positive</td>
</tr>
<tr>
<td>(initial cohort) Seiwert et al(^2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keynote-012</td>
<td>Pembrolizumab (200 mg q 3w)</td>
<td>Phase Ib single arm</td>
<td>Unselected PD-L1</td>
</tr>
<tr>
<td>(expansion cohort) Chow et al(^3)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## CheckMate141 & KEYNOTE012: A Breakthrough Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chemotherapy(^1) CheckMate 141 (n=121)</th>
<th>Nivolumab(^1) CheckMate 141 (n=240)</th>
<th>Pembrolizumab(^2) Phase 1b (n=56) KeyNOTE-12</th>
<th>Pembrolizumab(^3) Phase 1b (n=132) KeyNOTE-12 (EC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>5.8%</td>
<td>13.3%</td>
<td>18.0%</td>
<td>18.0%</td>
</tr>
<tr>
<td>CR</td>
<td>0.8%</td>
<td>2.5%</td>
<td>2.0%</td>
<td>3.0%</td>
</tr>
<tr>
<td>PR</td>
<td>5.0%</td>
<td>10.8%</td>
<td>16.0%</td>
<td>15.0%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>2.3 months</td>
<td>2.0 months</td>
<td>2.0 months</td>
<td>2.0 months</td>
</tr>
<tr>
<td>6-mo PFS</td>
<td>9.0%</td>
<td>19.7%</td>
<td>28.0%*</td>
<td>23.0%</td>
</tr>
<tr>
<td>Median OS</td>
<td>5.1 months</td>
<td>7.5 months</td>
<td>13.0 months</td>
<td>8.0 months</td>
</tr>
<tr>
<td>12-months</td>
<td>16.0%</td>
<td>36.0%</td>
<td>51.0%</td>
<td>37%*</td>
</tr>
</tbody>
</table>

\(^1\) From CheckMate 141 study (Ferris et al, NEJM 2016)

\(^2\) Seiwert et al, Lancet Oncol 2016; 17: 956-965

\(^3\) Chow et al, J Clin Oncol 2016; 34: 3838-3845

*Estimated from the survival curve
CheckMate 141: Overall Survival

CheckMate-141: Treatment-related Adverse Events

<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>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>5 (2.1)</td>
<td>14 (12.6)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>14 (12.6)</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>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>

CheckMate-141: Quality of Life and Symptom Burden

**Phase 3 KEYNOTE-040 Study (NCT02252042)**

**Key Eligibility Criteria**
- SCC of the oral cavity, oropharynx, hypopharynx, or larynx
- PD after platinum-containing regimen for R/M HNSCC or recurrence or PD within 3-6 mo of multimodal therapy using platinum
- ECOG PS 0 or 1
- Known p16 status (oropharynx)
- Tissue sample for PD-L1 assessment

**Stratification Factors**
- ECOG PS (0 vs 1)
- p16 status (positive vs negative)
- PD-L1 TPS (≥50% vs <50%)

**Pembrolizumab**
- 200 mg IV Q3W for 2 y

**Methotrexate**
- 40 mg/m² QW

**Docetaxel**
- 75 mg/m² Q3W

**Cetuximab**
- 250 mg/m² QW

- Clinically stable patients with radiologic PD could continue treatment until imaging performed ≥4 wk later confirmed PD
- Crossover not permitted

---

*Limit of 2 prior therapies for R/M HNSCC. bAssessed using the ClIntec p16 Histology assay (Ventana); cutpoint for positivity = 70%.

bNewly collected preferred. dAssessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. eCould be increased to 60 mg/m² QW in the absence of toxicity. fFollowing a loading dose of 400 mg/m².

Cohen EEW et al. Lancet Oncol, 2018
## Anti-PD-1 MoAb in Second-line R/M-SCCHN Level IA evidence (CM141&KN040)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Second-line Chemotherapy¹</th>
<th>Nivolumab Checkmate 141¹</th>
<th>Pembrolizumab KEYNOTE 040²</th>
<th>Second-line Chemotherapy²</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>5.8%</td>
<td>13.3%</td>
<td>14.6%</td>
<td>10.1%</td>
</tr>
<tr>
<td>CR</td>
<td>0.8%</td>
<td>2.5%</td>
<td>1.6%</td>
<td>0.4%</td>
</tr>
<tr>
<td>PR</td>
<td>5.0%</td>
<td>10.8%</td>
<td>13.0%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>2.3 months</td>
<td>2.0 months</td>
<td>2.1 months</td>
<td>2.3</td>
</tr>
<tr>
<td>6-month PFS</td>
<td>9.0%</td>
<td>19.7%</td>
<td>25.9%</td>
<td>19.5%</td>
</tr>
<tr>
<td>Median OS</td>
<td>5.1 months</td>
<td>7.5 months</td>
<td>8.4 months</td>
<td>7.1 months</td>
</tr>
<tr>
<td>12-months</td>
<td>16.6%</td>
<td>36.0%</td>
<td>37.3%</td>
<td>27.2%</td>
</tr>
</tbody>
</table>

CheckMate-141 vs KEYNOTE-040: median time to response 2.1 vs 4.5 months; response duration 9.7 vs 18.4 months

¹ From CheckMate 141 (Ferris et al, NEJM 2016)
Continuum of Care in Recurrent or Metastatic (R/M) Squamous Cell Carcinoma of the Head and Neck (SCCHN)

*EXTREME regimen (platinum, 5-FU, cetuximab) is supported by phase III data; TPE, cisplatin, docetaxel, cetuximab; PCE, carboplatin, paclitaxel, cetuximab

Modified from Argiris A et al. *Front Oncol.* 2017;7:72
## 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>IIIR</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>882</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* = tremelimumab (anti-CTLA-4); *Pembro* = pembrolizumab (anti-PD1)
KEYNOTE-048: A Breakthrough in 1st-Line?

KEYNOTE-048 Study Design (NCT02358031)

Key Eligibility Criteria
- SCC of the oropharynx, oral cavity, hypopharynx, or larynx
- R/M disease incurable by local therapies
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment
- Known p16 status in the oropharynx

Stratification Factors
- PD-L1 expression (TPS ≥50% vs <50%)
- p16 status in oropharynx (positive vs negative)
- ECOG performance status (0 vs 1)

Pembrolizumab 200 mg Q3W for up to 35 cycles

Pembrolizumab 200 mg + Carboplatin AUC 5 OR Cisplatin 100 mg/m² + 5-FU 1000 mg/m²/d for 4 days for 6 cycles (each 3 wk)

Cetuximab 250 mg/m² Q1W + Carboplatin AUC 5 OR Cisplatin 100 mg/m² + 5-FU 1000 mg/m²/d for 4 days for 6 cycles (each 3 wk)

Cetuximab 250 mg/m² Q1W

*Assessed using the PD-L1 IHC 22C3 pharmDX assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. **Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. Following a loading dose of 400 mg/m².
Overall Survival: P vs E, CPS ≥1 Population

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro alone</td>
<td>69%</td>
<td>0.78 (0.64-0.96)</td>
<td>0.0086</td>
</tr>
<tr>
<td>EXTREME</td>
<td>81%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

12-mo rate
51.0%
43.6%

24-mo rate
30.2%
18.6%

Median (95% CI)
12.3 mo (10.8-14.9)
10.3 mo (9.0-11.5)

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>257</th>
<th>196</th>
<th>152</th>
<th>110</th>
<th>74</th>
<th>34</th>
<th>17</th>
<th>2</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>255</td>
<td>207</td>
<td>152</td>
<td>110</td>
<td>74</td>
<td>34</td>
<td>17</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Data cutoff date: Jun 13, 2018.

Burtness B. et al Presented at ESMO, 22.10.2018
Overall Survival: P vs E, CPS ≥20 Population

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro alone</td>
<td>62%</td>
<td>0.61 (0.45-0.83)</td>
</tr>
<tr>
<td>EXTREME</td>
<td>78%</td>
<td></td>
</tr>
</tbody>
</table>

12-mo rate
56.9%
44.9%

24-mo rate
38.3%
22.1%

Median (95% CI)
14.9 mo (11.6-21.5)
10.7 mo (8.8-12.8)

No. at Risk
133 106 65 47 24 11 2 0
122 100 64 42 22 12 5 0

Data cutoff date: Jun 13, 2018.
## Overall Survival: P+C vs E, Total Population

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + Chemo</td>
<td>70%</td>
<td>0.77</td>
</tr>
<tr>
<td>EXTREME</td>
<td>80%</td>
<td>(0.63-0.93)</td>
</tr>
</tbody>
</table>

### Median (95% CI)
- Pembro + Chemo: 13.0 mo (10.9-14.7)
- EXTREME: 10.7 mo (9.3-11.7)

### 12-mo Rate
- Pembro + Chemo: 53.0%
- EXTREME: 43.9%

### 24-mo Rate
- Pembro + Chemo: 29.0%
- EXTREME: 18.7%

**No. at Risk**

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>281</td>
<td>227</td>
<td>169</td>
<td>122</td>
<td>75</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>1</td>
<td>278</td>
<td>227</td>
<td>147</td>
<td>100</td>
<td>51</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>47</td>
<td>47</td>
<td>47</td>
<td>47</td>
<td>47</td>
<td>47</td>
</tr>
</tbody>
</table>

Data cutoff date: Jun 13, 2018.

---

*Burtness B. et al Presented at ESMO, 22.10.2018*
EORTC 1559 - Umbrella trial: Personalized biomarker-based treatment strategy or immunotherapy in patients with recurrent/metastatic HNSCC «UPSTREAM»

Rachel Galot and Jean-Pascal Machiels, EORTC Meeting, Leipzig, 2017
Conclusions

• Discovery that CPIs can (re)activate the immune system of a patient against his/her own tumor: breakthrough

• There is a rapid evolution in systemic treatment in SCCHN, but many SCCHN patients will not benefit from this, therefore….

• Optimization of existing therapies needed (QA)

• Better patient selection for specific treatments

• Academic trials trials should get adequate support. Quality of life and symptom burden should get attention as endpoints.

• Precision medicine (with personalized approach) may be a new direction to explore
Thank you
7th Trends in Head and Neck Oncology

7–9 November 2019
Crowne Plaza Athens, Greece

www.THNO2019.org