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

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Conflict of Interest Disclosure

- 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
Milestones in Head and Neck Cancer Management

- **XIXème.**
- **1900**
- **1970s**
- **1980s**
- **1990s**
- **2000s**
- **2010**
- **2014**

- Surgery
- Radiotherapy
- X-rays
- Laser
- CT-scan
- MRI
- ASCO 1982
- Single agent chemotherapy → PF → TPF
- TORS
- IT
- MARCH
- MACH-NC

Courtesy of Jean-Louis Lefebvre
Milestones in Systemic Therapies (± RT) in Head and Neck Squamous Cell Cancer

1960s
- Single agent chemotherapy
  - Methotrexate

1970s
- Combination chemotherapy regimens
  - Platinum compounds

1980s
- Larynx preservation
- Induction chemotherapy (ICT)

1990s
- Concurrent CRT standard (CCRT)
  - Taxanes

2000s
- De-escalation trials in HPV+ OPC
- ICT revisited
- Targeted therapy / Immunotherapy
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: larynxpreservation; BRT: bioradiotherapy; LT: local treatment; ST: systemic treatment; TT: targeted therapy; RT: radiotherapy; PS: performance status

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*except for those unable to tolerate standard therapy due to co-morbidity or poor PS
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)
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*except for those unable to tolerate standard therapy due to co-morbidity or poor PS
<table>
<thead>
<tr>
<th>Treatment 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></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 CCRT

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
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

Guidelines Clinical trials

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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 cisplatin\(^1\)
  - Both high- and low-dose regimens excluded
  - Carboplatin/5-FU schedule (GORTEC)\(^2\)
  - Cetuximab\(^3\), docetaxel/cetuximab
  - Radiotherapy alone

• Relative contra-indications to cisplatin\(^1\) (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

\(^1\)Ahn et al. Oral Oncol 2016; \(^2\)Denis et al, J Clin Oncol 2004; \(^3\)Bonner et al, NEJM 2006
\* 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


Trial Design - W3W

**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 LNIs +
- 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**

**Weekly vs 3-weekly cisplatin**
- 3-weekly cisplatin: 100mg/m² D1,2,3 of RT
- Weekly cisplatin: 30mg/m² with RT

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

**Chemotherapy Details**

<table>
<thead>
<tr>
<th>Weekly cisplatin (n=150)</th>
<th>3-wkly cisplatin (n=150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycles of chemotherapy-no. (%)</td>
<td>5: 17 (11.3)</td>
</tr>
<tr>
<td>Days from surgery to CRT start (n=276)-Median (IQR)</td>
<td>&gt;6.133 (88.7)</td>
</tr>
<tr>
<td>Total treatment time in days (n=276)-Median (IQR)</td>
<td>85 (79-96)</td>
</tr>
<tr>
<td>Dose reduction in chemotherapy-no. (%)</td>
<td>Yes 14 (9.3)</td>
</tr>
<tr>
<td>No 136 (90.7)</td>
<td>138 (92)</td>
</tr>
<tr>
<td>Dose delay &gt; 2 days-no. (%)</td>
<td>Yes 37 (24.7)</td>
</tr>
<tr>
<td>No 113 (75.3)</td>
<td>108 (72)</td>
</tr>
<tr>
<td>Days between planned and actual chemo cycle-median (IQR)</td>
<td>0 (0-3)</td>
</tr>
<tr>
<td>Cumulative cisplatin dose in mg/m² - Median (IQR)</td>
<td>210 (180-210)</td>
</tr>
</tbody>
</table>

Follow-up: Weekly during CRT, then Q3 mths x 2 yrs, then Q6 mths
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></th>
<th></th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CET</td>
<td>CIS</td>
<td>HR</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>Unadjusted (n=3.986)</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>PS matched (n=2.114)</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>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>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>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*</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>

*PS matched

Baumüllner J, et al. ASCO 2018; abstract #6073
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
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
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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></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>Grose et al 1985</td>
<td>100</td>
<td>Methotrexate, Cisplatin</td>
<td>16, 8</td>
<td>5.0, 4.5</td>
<td>No</td>
</tr>
<tr>
<td>Forastiere et al 1992</td>
<td>277</td>
<td>Cisplatin + 5-FU, Carboplatin + 5-FU, Methotrexate</td>
<td>32*, 21, 10</td>
<td>6.6, 5.0, 5.6</td>
<td>No</td>
</tr>
<tr>
<td>Clavel et al 1994</td>
<td>382</td>
<td>CABO, Cisplatin + 5-FU, Cisplatin</td>
<td>34*, 31*, 15</td>
<td>7.3, 7.3, 7.3</td>
<td>No</td>
</tr>
<tr>
<td>Gibson et al 2005</td>
<td>218</td>
<td>Cisplatin + 5-FU, Cisplatin + paclitaxel</td>
<td>27, 26</td>
<td>8.7, 8.1</td>
<td>No</td>
</tr>
<tr>
<td>Vermorken et al 2008</td>
<td>442</td>
<td>Platinum + 5-FU, Platinum + 5-FU + Cetuximab</td>
<td>20, 36*</td>
<td>7.4, 10.1*</td>
<td>Yes</td>
</tr>
</tbody>
</table>

CABO, cisplatin, methotrexate, bleomycin, vincristine

*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</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>PF(^1)</td>
<td>20</td>
<td>3.3</td>
<td>7.4</td>
</tr>
<tr>
<td>SPECTRUM</td>
<td>657</td>
<td>PF(^2) + panitumumab</td>
<td>36(^a)</td>
<td>5.8(^b)</td>
<td>11.1</td>
</tr>
<tr>
<td>Vermorken et al</td>
<td></td>
<td>PF(^2)</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</td>
<td>36(^a)</td>
<td>6.1(^b)</td>
<td>12.6</td>
</tr>
<tr>
<td>Argiris et al</td>
<td></td>
<td>4 Pt doublets(^3)</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>

\[^{a, b, c}a, b, c:\text{significant differences}\]  
\[^{3}PF\text{ or } PT\text{ both with or without bevacizumab}\]
EXTREME: A Breakthrough in First-line R/M-SCCHN

N=442

R/M SCCHN
- Prior CT
- KPS (<80 vs ≥80)

CT
Cisplatin (100 mg/m² IV, day 1) or Carboplatin (AUC 5, day 1) + 5-FU (1000 mg/m² IV, days 1–4)
Every 3 weeks, up to 6 cycles

cetuximab
Initial dose 400 mg/m²
then 250 mg/m² weekly
until progressive disease (PD)

Primary endpoint: OS
Secondary endpoints: PFS, RR, safety

Vermorken et al. NEJM 2008
Cetuximab added to Chemotherapy Improves Overall Survival in Recurrent/Metastatic SCCHN

*Chemotherapy consisted of cisplatin/carboplatin + 5-FU

EXTREME – Overall Survival
Long-term follow-up

Vermorken et al. ASCO 2014 (abstr. #6021)
### Phase III Trials in 2nd Line R/M-SCCHN
#### Anti-EGFR therapy vs chemotherapy

<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>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></td>
<td></td>
<td>D + Placebo</td>
<td>6</td>
<td>2.1 (TTP)</td>
<td>6.0</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
## LUX-HN1: Adverse Events Overall Summary

<table>
<thead>
<tr>
<th></th>
<th>Overall population</th>
<th>Patients ≥65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Afatinib (n=320)</td>
<td>MTX (n=160)</td>
</tr>
<tr>
<td>Any AEs, n (%)</td>
<td>318 (99)</td>
<td>158 (99)</td>
</tr>
<tr>
<td>Drug-related AEs, n (%)</td>
<td>303 (95)</td>
<td>137 (86)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>127 (40)</td>
<td>57 (36)</td>
</tr>
<tr>
<td>Leading to dose reduction</td>
<td>103 (32)</td>
<td>67 (42)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>23 (7)</td>
<td>26 (16)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>44 (14)</td>
<td>18 (11)</td>
</tr>
<tr>
<td>Leading to death</td>
<td>2 (0.6)*</td>
<td>5 (3)†</td>
</tr>
<tr>
<td>Treatment duration, median (range)</td>
<td>83 (2–546)</td>
<td>43 (1–442)</td>
</tr>
</tbody>
</table>

*One septic shock and one aspiration pneumonia
†Two septicaemia, one aspiration pneumonia, one general health deterioration, and one renal failure and pancytopenia
‡Renal failure and pancytopenia
<table>
<thead>
<tr>
<th>Immune Checkpoint Inhibitors (ICIs) Under Development for R/M-SCCHN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Nivolumab</strong></td>
</tr>
<tr>
<td>- IgG4</td>
</tr>
<tr>
<td>- Fully human</td>
</tr>
<tr>
<td>- High Affinity for PD-1 (KD ~ 2.6 nM)</td>
</tr>
<tr>
<td><strong>2. Pembrolizumab</strong></td>
</tr>
<tr>
<td>- IgG4</td>
</tr>
<tr>
<td>- Humanized</td>
</tr>
<tr>
<td>- High Affinity for PD-1 (KD ~ 29 pM)</td>
</tr>
<tr>
<td><strong>3. Other PD-1/PD-L1 agents in development:</strong></td>
</tr>
<tr>
<td>- PD-L1 agents – Atezolizumab (IgG1), Durvalumab (IgG1), Avelumab (IgG1)</td>
</tr>
<tr>
<td><strong>4. CTLA-4 agents:</strong></td>
</tr>
<tr>
<td>- Ipilimumab (IgG1), Tremelimumab (IgG2)</td>
</tr>
</tbody>
</table>

*Courtesy from Seiwert (modified)*
# Clinical Trials with PD-1 Inhibitors Leading to Approval for Patients with 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 (initial cohort)</td>
<td>Pembrolizumab (10 mg/kg q 2w)</td>
<td>Phase Ib single arm</td>
<td>PD-L1 positive</td>
</tr>
<tr>
<td>Seiwert et al(^2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keynote-012 (expansion cohort)</td>
<td>Pembrolizumab (200 mg q 3w)</td>
<td>Phase Ib single arm</td>
<td>Unselected PD-L1</td>
</tr>
<tr>
<td>Chow et al(^3)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Anti-PD-1 MoAb in Second-line R/M-SCCHN

### Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chemother(^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>16.6%</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

<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)
36.0% (28.5, 43.4)
16.6% (8.6, 26.8)

## 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></td>
<td>Any Grade n (%)</td>
<td>Grade 3–4 n (%)</td>
</tr>
<tr>
<td>Any treatment-related AE in ≥10% of patients(^8)</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>

---

CheckMate-141: Quality of Life and Symptom Burden

# Studies with Immune Checkpoint Inhibitors in Platinum-pretreated R/M-SCCHN

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug(s)</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>CheckMate-714</td>
<td>Nivolumab (N) + ipilimumab vs N + placebo</td>
<td>II</td>
</tr>
<tr>
<td>KEYNOTE-055</td>
<td>Pembrolizumab monotherapy</td>
<td>II</td>
</tr>
<tr>
<td>KEYNOTE-040</td>
<td>Pembrolizumab vs IC</td>
<td>III</td>
</tr>
<tr>
<td>CONDOR</td>
<td>Durvalumab (D), tremelimumab or combo</td>
<td>II</td>
</tr>
<tr>
<td>EAGLE</td>
<td>Durvalumab (D) vs D+tremelimumab vs IC</td>
<td>III</td>
</tr>
<tr>
<td>HAWK</td>
<td>Durvalumab monotherapy</td>
<td>II</td>
</tr>
<tr>
<td>EACH</td>
<td>Avelumab vs avelumab + cetuximab</td>
<td>II</td>
</tr>
<tr>
<td>CONFRONT</td>
<td>Avelumab + cyclophosphamidane +RT</td>
<td>I/II</td>
</tr>
<tr>
<td>NCT03260023</td>
<td>Avelumab + TG4001</td>
<td>Ib/II</td>
</tr>
<tr>
<td>ATHENA</td>
<td>Atezolizumab + bevacizumab</td>
<td>II</td>
</tr>
<tr>
<td>QUILT-3.055</td>
<td>ICI + ALT-803</td>
<td>IIb</td>
</tr>
</tbody>
</table>

*IC = investigator's choice*
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\(^a\)
- ECOG PS 0 or 1
- Known p16 status (oropharynx)\(^b\)
- Tissue sample\(^c\) for PD-L1 assessment\(^d\)

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

R 1:1

Pembrolizumab
200 mg IV Q3W for 2 y

Methotrexate 40 mg/m\(^2\) QW\(^e\)
OR
Docetaxel 75 mg/m\(^2\) Q3W
OR
Cetuximab 250 mg/m\(^2\) QW\(^f\)

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

\(^a\) Limit of 2 prior therapies for R/M HNSCC
\(^b\) Assessed using the CIntec p16 Histology assay (Ventana); cutpoint for positivity = 70%
\(^c\) Newly collected preferred
\(^d\) Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies). TPS = tumor proportion score = % of tumor cells with membraneous PD-L1 expression
\(^e\) Could be increased to 60 mg/m\(^2\) QW in the absence of toxicity
\(^f\) Following a loading dose of 400 mg/m\(^2\)

Cohen EEW et al. Lancet Oncol, 2018
Overall Survival: Intention-to-Treat Population

Cohen EEW et al. Lancet Oncol, 2018

A) PD-L1 combined positive score = 1
   - Pembrolizumab
   - Standard of care
   - HR 0.74 (95% CI 0.58–0.93); nominal p=0.0049

B) PD-L1 combined positive score > 1
   - HR 1.28 (95% CI 0.80–2.07); nominal p=0.476

C) PD-L1 tumour proportion score > 50%
   - HR 0.53 (95% CI 0.35–0.81); nominal p=0.0014

D) PD-L1 tumour proportion score ≤ 50%
   - HR 0.93 (95% CI 0.73–1.17); nominal p=0.2675

Cohen EEW et al. Lancet Oncol, 2018
Do not duplicate or distribute without permission from author and ESO
KEYNOTE-040: Adverse Events

Treatment-Related AEs With Incidence ≥10%

Immune-Mediated AEs

Cohen et al, presented at ESMO 2017
## Comparison Between CheckMate-141 and KEYNOTE-040 Phase III Trials in 2nd Line Recurrent/Metastatic SCCHN: Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Second-line Chemother&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Nivolumab CheckMate 141&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Pembrolizumab KEYNOTE 040&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Second-line Chemother&lt;sup&gt;2&lt;/sup&gt;</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>37.0%</td>
<td>26.5%</td>
</tr>
</tbody>
</table>

<sup>*CheckMate-141 vs KEYNOTE-040: median time to response 2.1 vs 4.5 months; response duration 9.7 vs 18.4 months</sup>

<sup>1 From CheckMate 141 (Ferris et al, NEJM 2016)</sup>

<sup>2 From KEYNOTE-040 (Cohen et al, ESMO abstract LBA-45, 2017 and Lancet Oncol 2018)"</sup>
## Comparison Between CheckMate-141 and KEYNOTE-040 in 2nd Line R/M-SCCHN

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CheckMate-141</th>
<th>KEYNOTE-040</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion period</td>
<td>06/2014 - 08/2015</td>
<td>12/2014 – 05/2016</td>
</tr>
<tr>
<td>Number of patients</td>
<td>361</td>
<td>495</td>
</tr>
<tr>
<td>Patient selection</td>
<td>PD &lt; 6 mo after platinum</td>
<td>PD within 3-6 mo after Pt-based CT or PD after 1st or 2nd line platinum</td>
</tr>
<tr>
<td>Different SoC arm</td>
<td>MTX, cet, wkly doce</td>
<td>MTX, cet, 3-wkly doce</td>
</tr>
<tr>
<td>Subsequent ICIs in SoC</td>
<td>9.1% (11 of 121)*</td>
<td>12.5% (31 of 248)**</td>
</tr>
<tr>
<td>PD-L1 expression</td>
<td>TPS (≥1% vs &lt;1%)</td>
<td>CPS (≥1 vs &lt;1)</td>
</tr>
<tr>
<td></td>
<td>HR 0.55; median OS 8.7 mo</td>
<td>HR 0.74; median OS 8.7 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TPS≥50%; HR 0.53 and median OS 11.6 months</td>
</tr>
</tbody>
</table>

* Pai et al. JITS 2019 (in review)  
  ** Ferris et al. Oral Oncol 2018  
  **Cohen et al, Lancet Oncol 2018
Continuum of Care in Recurrent or Metastatic (R/M) Squamous Cell Carcinoma of the Head and Neck (SCCHN)

1st line (including relapses >6 mo post RT/platinum)
- With EXTREME: median OS 10.1 months; 2-year OS 14%

2nd and later line
- Cetuximab + chemo-based regimen* (EXTREME†, TPE, PCE)
  - Checkpoint inhibitor monotherapy
  - Clinical Trial
  - Single-agent chemotherapy or Targeted therapy or Combination

*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 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\(^a\)
- Known p16 status in the oropharynx\(^b\)

**Pembrolizumab Monotherapy**
- Pembrolizumab 200 mg Q3W for up to 35 cycles

**Pembrolizumab + Chemotherapy**
- Pembrolizumab 200 mg + Carboplatin AUC 5 OR Cisplatin 100 mg/m\(^2\) + 5-FU 1000 mg/m\(^2\)/d for 4 days for 6 cycles (each 3 wk)

**EXTREME**
- Cetuximab 250 mg/m\(^2\) Q1W\(^c\) + Carboplatin AUC 5 OR Cisplatin 100 mg/m\(^2\) + 5-FU 1000 mg/m\(^2\)/d for 4 days for 6 cycles (each 3 wk)

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

---

\(^a\)Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression.  
\(^b\)Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%.  
\(^c\)Following a loading dose of 400 mg/m\(^2\).
## Overall Survival: P vs E, CPS ≥1 Population

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>EXTREME</td>
<td>81%</td>
<td></td>
</tr>
</tbody>
</table>

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

**No. at Risk**
- 257
- 255
- 196
- 152
- 131
- 110
- 89
- 74
- 47
- 34
- 21
- 9
- 2
- 1
- 0

Data cutoff date: Jun 13, 2018.
Overall Survival: P vs E, CPS ≥20 Population

- **Events**
  - Pembro alone: 62%
  - EXTREME: 78%

- **HR (95% CI) and P**
  - Pembro alone: 0.61 (0.45-0.83) 0.0007

- **24-mo rate**
  - Pembro alone: 38.3%
  - EXTREME: 22.1%

- **12-mo rate**
  - Pembro alone: 56.9%
  - EXTREME: 44.9%

- **Median (95% CI)**
  - Pembro alone: 14.9 mo (11.6-21.5)
  - EXTREME: 10.7 mo (8.8-12.8)

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>

12-mo rate:
- Pembro + Chemo: 53.0%
- EXTREME: 43.9%

24-mo rate:
- Pembro + Chemo: 29.0%
- EXTREME: 18.7%

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

Data cutoff date: Jun 13, 2018.
EORTC 1559 - Umbrella trial: Personalized biomarker-based treatment strategy or immunotherapy in patients with recurrent/metastatic HNSCC «UPSTREAM»

**Diagram Description:**

- **Patients with recurrent/metastatic SCCHN, progressive after platinum-based therapy**
  - Primary consent and screening eligibility
  - Biopsy with sequencing of targeted genes and IHC
    - **Immunotherapy patient cohorts**
      - Cohort I1: Monalizumab
      - Cohort I2: Randomization 2:1:1
        - Monalizumab
        - Monalizumab + Durvalumab
        - Best treatment of choice
    - **Biomarker-driven patient cohorts**
      - Cohort B1: p16 neg and EGFR amplification/mutation or PTEN high or HER2 amplification/mutation
        - Randomization 2:1
        - Best treatment of choice
      - Cohort B2: p16 neg and cetuximab naive
        - Randomization 2:1
        - Best treatment of choice
      - Cohort B3: p16 neg and CCND1 amplification
        - Randomization 2:1
        - Best treatment of choice
      - Cohort B4: p16 neg and 'platinum-sensitive'
      - Cohort B5: p16 pos oropharyngeal cancer
      - Cohort B6: ROS1 and NTRK gene fusions
        - Niraparib
        - Entrectinib

**Informed consent must be taken at 2 timepoints:**
1. At registration
2. After allocation to patient cohort and before randomization, when applicable (★ in the scheme)

*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 in this highly competitive field

- **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
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

Stratification factor
- Prior cetuximab treatment

R 2:1

Nivolumab
3 mg/kg IV q 2 w

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

Primary endpoint
- OS

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

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

CheckMate-141: Overall Survival by Tumor PD-L1 Expression (at 1%)
CheckMate 141: OS in Patients with PD < 6 Months after Platinum for Curative Therapy

ORR: 19.2 vs 11.5%

Gillison et al. ASCO 2017

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CheckMate 141: Efficacy Analysis by Age

Saba et al. ASCO 2018 (poster 6028)
# CheckMate 141: Toxicity Analysis by Age

<table>
<thead>
<tr>
<th></th>
<th>&lt;65 years</th>
<th></th>
<th>≥65 years</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivolumab (n = 168)</td>
<td>IC (n = 71)</td>
<td>Nivolumab (n = 68)</td>
<td>IC (n = 40)</td>
</tr>
<tr>
<td><strong>Any grade</strong></td>
<td>Any grade</td>
<td>Grade 3–4</td>
<td>Any grade</td>
<td>Grade 3–4</td>
</tr>
<tr>
<td><strong>Any TRAE, n (%)</strong></td>
<td>107 (63.7)</td>
<td>27 (16.1)</td>
<td>55 (77.5)</td>
<td>22 (31.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24 (14.3)</td>
<td>3 (1.8)</td>
<td>14 (19.7)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>17 (10.1)</td>
<td>0</td>
<td>16 (22.5)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Rash</td>
<td>14 (8.3)</td>
<td>0</td>
<td>1 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13 (7.7)</td>
<td>1 (0.6)</td>
<td>7 (9.9)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>11 (6.5)</td>
<td>0</td>
<td>6 (8.5)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>8 (4.8)</td>
<td>2 (1.2)</td>
<td>13 (18.3)</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>8 (4.8)</td>
<td>0</td>
<td>12 (16.9)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (3.6)</td>
<td>0</td>
<td>4 (5.6)</td>
<td>0</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>4 (2.4)</td>
<td>0</td>
<td>9 (12.7)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>2 (1.2)</td>
<td>1 (0.6)</td>
<td>8 (11.3)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>0</td>
<td>10 (14.1)</td>
<td>0</td>
</tr>
</tbody>
</table>

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