RECURRENT SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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Brussels, Belgium
DISCLOSURE OF INTEREST

Advisory role: MSD (uncompensated), Innate, Debio, Astra-Zeneca, Nanobiotix

Research grants: Novartis, Janssen.
• **Diagnosis**

• Prognosis

• Lung metastases: surgery?

• Re-irradiation and salvage surgery

• Chemotherapy

• Molecular biology and targeted therapies

• Immunotherapy
Diagnosis

• Between 40-60% of patients will relapse in the head and neck area without distant metastases.

• Imaging sometimes difficult due to the morphological modification of the local tissues induced by previous surgery and/or (chemo)radiation.

• The differential diagnosis includes radionecrosis, infection, and scar from previous treatment(s).

• **Effort should be made to obtain pathological confirmation**

• PET/scan
• Diagnosis

• **Prognosis**

• Lung metastases: surgery?

• Re-irradiation and salvage surgery

• Chemotherapy

• Molecular biology and targeted therapies

• Immunotherapy
Prognosis

Prognostic factors in patients with recurrent or metastatic SCCHN treated with cisplatin-based chemotherapy in two phase III trials (E1393 and E1395)

<table>
<thead>
<tr>
<th>Prognostic factors for poor survival in the multivariate analysis (n=399)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss &gt; 5%</td>
<td>0.0004</td>
</tr>
<tr>
<td>ECOG 1 vs 0</td>
<td>0.0016</td>
</tr>
<tr>
<td>Well and moderate differentiation</td>
<td>0.028</td>
</tr>
<tr>
<td>Primary tumor oral cavity or hypopharynx</td>
<td>0.011</td>
</tr>
<tr>
<td>Prior radiation therapy</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- 0-2 unfavorable prognostic factors: median OS = one year.
- 3-5 unfavorable prognostic factors: median OS = six months (p < 0.0001)
Prognosis: p16 and recurrent disease

Carole Fakhry et al. JCO 2014;32:3365-3373

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Prognosis: p16 and recurrent disease

Locoregional relapse

Distant metastases

Salvage surgery

No salvage surgery

Fakhry et al. J Clin Oncol 2014
Prognosis

Other prognostic factors included:

- comorbidity
- ongoing tobacco and alcohol use
- hypercalcemia
- response to prior treatment
- social support

Colevas AD, JCO, 2006
• Diagnosis
• Prognosis
• **Lung metastases: surgery?**
• Re-irradiation and salvage surgery
• Chemotherapy
• Molecular biology and targeted therapies
• Immunotherapy

*Pivot et al, Oncology, 2001*
• The differential diagnosis must be made taking with a second primary cancer, particularly if curative treatment can be proposed.

• The rate of synchronous pulmonary tumors is around 4%

• The overall incidence of metachronous second primary cancers is 2% per year.

• The 5-year survival after pulmonary metastasectomy: 26.5-59.5%

• It is reasonable to recommend lung resection
  - for a single cancerous lung nodule.

• For two or more lung metastases: to be discussed within a multidisciplinary team.
• Diagnosis
• Prognosis
• Lung metastases: surgery?
• **Re-irradiation and salvage surgery**
• Chemotherapy
• Molecular biology and targeted therapies
• Immunotherapy

*Pivot et al, Oncology, 2001*
• Between 20-57% of patients treated with radiation therapy will develop local and/or regional relapse

• Re-irradiation and salvage surgery: discuss within the multidisciplinary team
The 5-year survival after pulmonary metastasectomy: 26.5-59.5%

It is reasonable to recommend lung resection - for a single cancerous lung nodule.

For two or more lung metastases: to be discussed within a multidisciplinary team.

(Re)irradiation or salvage surgery
(Re)irradiation or salvage surgery

1. The 5-year survival after pulmonary metastasectomy: 26.5-59.5%
2. It is reasonable to recommend lung resection for a single cancerous lung nodule.
3. For two or more lung metastases: to be discussed within a multidisciplinary team.

---

**TREATMENT OF HEAD AND NECK CANCER**

- **Locoregional recurrence without prior RT**
  - Resectable:
    - No adverse features
    - Extracapsular spread and/or positive margin
  - Adverse features:
    - Other risk features
    - Surgery
    - Systemic therapy/RT
  - Unresectable:
    - Systemic therapy/RT
    - Salvage therapy for persistent disease as indicated
- **Recurrent or Persistent disease**
  - Locoregional recurrence or second primary with prior RT
  - Resectable:
    - Surgery
    - Reirradiation ± systemic therapy, clinical trial preferred
  - Unresectable:
    - Systemic therapy ± systemic therapy, clinical trial preferred
    - Best supportive care
- **Distant metastases**
  - See (ADV-4)
The 5-year survival after pulmonary metastasectomy: 26.5-59.5%

It is reasonable to recommend lung resection for a single cancerous lung nodule. For two or more lung metastases: to be discussed within a multidisciplinary team.

(Re)irradiation or salvage surgery

(Re)irradiation or salvage surgery
• Diagnosis

• Prognosis

• Lung metastases: surgery?

• Re-irradiation and salvage surgery

• **Chemotherapy**

• Molecular biology and targeted therapies

• Immunotherapy
## Single-agent response rate

<table>
<thead>
<tr>
<th>Drug</th>
<th>Response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>14-41%</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>20-30%</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>10%</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>8-77%</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>15%</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>8%</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>21-42%</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>13-40%</td>
</tr>
</tbody>
</table>
Randomized trials chemotherapy versus BSC

- One trial:
  - BSC (n=26) versus bleomycin (n=22) versus cisplatin (n=38) versus cisplatin plus bleomycin (n=30).

- The conclusions were
  - cisplatin improved survival compared with BSC by 10 weeks
  - cisplatin was better than bleomycin or methotrexate
  - cisplatin monotherapy (median survival: 160 days) was at least as effective as the platinum-based combinations.
Randomized trials chemotherapy versus BSC

N=200

Cisplatin vs methotrexate (p=0.025)

Figure 1  Survival curves of all four groups.

The Liverpool head and neck oncology group. BJC 1990
### Randomized trials mono vs polychemotherapy

<table>
<thead>
<tr>
<th>Regimens</th>
<th>N</th>
<th>ORR (%)</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin/5-FU vs Cisplatin vs 5-FU</td>
<td>249</td>
<td>32%</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17%</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13%</td>
<td>6.1</td>
</tr>
<tr>
<td>Cisplatin/methotrexate/bleomycine/vincristine vs Cisplatin/5-FU vs Cisplatin</td>
<td>382</td>
<td>34%</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31%</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15%</td>
<td>5.3</td>
</tr>
</tbody>
</table>

## Randomized trials mono vs polychemotherapy

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<th>N</th>
<th>ORR (%)</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin/5-FU vs Carboplatin/5-FU vs Methotrexate</td>
<td>277</td>
<td>32%</td>
<td>6.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21%</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10%</td>
<td>5.6</td>
</tr>
<tr>
<td><em>Cisplatin/pemetrexed</em> vs Cisplatin</td>
<td>795</td>
<td>12.1%</td>
<td>7.3*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.1%</td>
<td>6.3</td>
</tr>
</tbody>
</table>

* ECOG 0-1:  
  OS (8.4 vs 6.7 months; p=0.026)  
  Oropharyngeal: OS (9.9 vs 6.1 months; p=0.002)

Randomized trials with taxanes

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<th>N</th>
<th>ORR (%)</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin/5-FU</td>
<td>218</td>
<td>27%</td>
<td>8.7</td>
</tr>
<tr>
<td>versus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin/paclitaxel</td>
<td></td>
<td>26%</td>
<td>8.1</td>
</tr>
</tbody>
</table>

- Cisplatin (100 mg/m2, day 1)/5-FU (1000 mg/m2/d, day 1-4), every 3 weeks
- Cisplatin (75 mg/m2, day 1)/paclitaxel (175 mg/m2, day 1), every 3 weeks

Gibson et al JCO 2005
Chemotherapy: conclusions

- Median survival of patients is 6-8 months
- No evidence that chemotherapy prolongs survival

Polychemotherapy versus monochemotherapy:
- Higher response rate
- More toxic
- No improvement in survival

- Cisplatin /5-FU
- Cisplatin /paclitaxel
- Methotrexate (40 mg/m2/every week)
• Diagnosis
• Prognosis
• Lung metastases: surgery?
• Re-irradiation and salvage surgery
• Chemotherapy

• **Molecular biology and targeted therapies**
• Immunotherapy

*Pivot et al, Oncology, 2001*
Monoclonal Antibodies
Cetuximab
Panitumumab
Zalutumumab

Tyrosine kinase Inhibitors
Gefitinib (EGFR)
Erlotinib (EGFR)
Lapatinib (EGFR + HER2)
Afatinib, dacomitinib (pan-HER)

Tumor cell cytoplasmic membrane

EGF receptor

Tumor proliferation
- Anti-EGFR first-line palliative treatment: mAbs
- Anti-EGFR second line: mAbs and TKIs
Platin/5-FU vs platin/5-FU plus cetuximab

EXTREME Trial: first line palliative treatment

N= 442

Primary endpoint: survival

Vermorken et al, NEJM, 2008
Patients at Risk

Survival Time [Months]

CTX only CET + CTX

220 173 127 83 65 47 19 8 1222 184 153 118 82 57 30 15 3

HR (95%CI): 0.797 (0.644, 0.986) Strat. log-rank test: 0.0362

CTX only

Cetuximab + CTX

Survival Probability

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

0 3 6 9 12 15 18 21 24

10.1 mo

7.4 mo

Vermorken et al, NEJM 2008
These regimens can be TOXIC
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Regimens</th>
<th>Median PFS</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vermorken NEJM 2008</td>
<td>220</td>
<td>Platin/5-Fluorouracil <strong>versus</strong> Platin/5-FU/cetuximab</td>
<td>3.3 months*</td>
<td>7.4 months*</td>
</tr>
<tr>
<td></td>
<td>222</td>
<td></td>
<td>5.6 months*</td>
<td>10.1 months*</td>
</tr>
<tr>
<td>Vermorken Lancet Oncol</td>
<td>330</td>
<td>Cisplatin/5-Fluorouracil <strong>versus</strong> Cisplatin/5-FU/panitumumab</td>
<td>4.6 months*</td>
<td>9 months</td>
</tr>
<tr>
<td></td>
<td>327</td>
<td></td>
<td>5.8 months*</td>
<td>11.1 months</td>
</tr>
</tbody>
</table>

* Statistically significant
. Anti-EGFR first-line palliative treatment: mAbs

. Anti-EGFR second line: mAbs and TKIs
Anti-EGFR monoclonal antibodies

Platinum-5FU + anti-EGFR
6 chemotherapy cycles → anti-EGFR moAbs monotherapy
until PD or toxicity

Platinum-based CT
6 chemotherapy cycles → anti-EGFR moAbs monotherapy
at PD

What is the best option?
Pooled of three prospective phase II trials with cetuximab monotherapy or with platin (N=278)

Retrospective study of patients who received various second-line treatments (N=194)

5.2 - 6.1 months
3.4 – 3.6 months

FDA approval

Vermorken et al. Cancer 2008
Anti-EGFR failed in second-line

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Regimens</th>
<th>ORR</th>
<th>Median PFS</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stewart JCO 2009</td>
<td></td>
<td>Methotrexate <em>versus</em> Gefitinib 250 mg/day <em>versus</em> Gefitinib 500 mg/day</td>
<td>3.9%</td>
<td>NA</td>
<td>5.6 months</td>
</tr>
<tr>
<td></td>
<td>161</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>158</td>
<td></td>
<td>2.7%</td>
<td>NA</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>167</td>
<td></td>
<td>7.6%</td>
<td></td>
<td>6.7 months</td>
</tr>
<tr>
<td>Argiris JCO 2009</td>
<td></td>
<td>Docetaxel + placebo <em>versus</em> Docetaxel + gefitinib</td>
<td>6.2%</td>
<td>NA</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>136</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>134</td>
<td></td>
<td>12.5%</td>
<td></td>
<td>7.3 months</td>
</tr>
<tr>
<td>Machiels Lancet Oncol 2011</td>
<td>95</td>
<td>BSC or methotrexate <em>versus</em> Zalutumumab</td>
<td>1.1%</td>
<td>8.4 weeks</td>
<td>5.2 months</td>
</tr>
<tr>
<td></td>
<td>191</td>
<td></td>
<td>6.3%</td>
<td>9.9 weeks*</td>
<td>6.7 months</td>
</tr>
</tbody>
</table>

* Statistically significant
MEHD7945A

- EGFR
- HER-2
- HER-3
- HER-4

Lapatinib
Afatinib
Dacomititimb
# EGFR/HER3 or pan-HER inhibition

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Regimens</th>
<th>ORR</th>
<th>Median PFS</th>
<th>Median Survival</th>
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</thead>
<tbody>
<tr>
<td>Fayette ESMO LBA 2014</td>
<td>62</td>
<td>Cetuximab versus MEHD7945A</td>
<td>14.5%</td>
<td>4 months</td>
<td>8.5 months</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td></td>
<td>11.9%</td>
<td>4.1 months</td>
<td>7.2 months</td>
</tr>
<tr>
<td>Machiels** Lancet Oncol 2015</td>
<td>161</td>
<td>Methotrexate versus Afatinib</td>
<td>5.6%</td>
<td>1.7 months</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>322</td>
<td></td>
<td>10.2%</td>
<td>2.6 months*</td>
<td>6.8 months</td>
</tr>
</tbody>
</table>

* Statistically significant
** Previous used of cetuximab allowed
<table>
<thead>
<tr>
<th>EGFR overexpression:</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR polysomy or amplification:</td>
<td>NO</td>
</tr>
<tr>
<td>K-ras mutations</td>
<td>Rare in H&amp;N</td>
</tr>
<tr>
<td>p16 or HPV</td>
<td>?</td>
</tr>
</tbody>
</table>

Licitra et al, Annals of Oncology 2010
### Who is going to response? HPV or p16 no clear answer

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Population</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenthal ASCO 2014</td>
<td>Radiotherapy/ cetuximab</td>
<td>p16+ = 44; p16- = 109</td>
<td>Stage III/IV</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy</td>
<td>p16+ = 39; p16- = 120</td>
<td>p16- : HR: 0.9 (OS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p16+ : HR: 0.45</td>
</tr>
<tr>
<td>Vermorken Ann Oncol 2014</td>
<td>Platin/5-FU/Cetuximab</td>
<td>p16+ = 18; p16- = 178</td>
<td>Recurrent/metastatic: first-line</td>
</tr>
<tr>
<td></td>
<td>Platin/5-FU</td>
<td>p16+ = 23; p16- = 162</td>
<td>p16- : HR: 0.82 (OS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p16+ : HR: 0.63</td>
</tr>
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</tr>
<tr>
<td></td>
<td>Platin/5-FU</td>
<td>p16+ = 42; p16- = 165</td>
<td>p16- : HR: 0.73 (OS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p16+ : HR: 1</td>
</tr>
<tr>
<td>Machiels Lancet Oncol 2015</td>
<td>Afatinib Methotrexate</td>
<td>p16+ = 31; p16- =141</td>
<td>Recurrent/metastatic second-line</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p16+ = 11; p16- = 42</td>
<td>p16- : HR: 0.69 (PFS)</td>
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</table>
Cetuximab vs MEHD after platinum

Measures of HER3 activation correspond with tumor shrinkage in both treatment arms.

A. An inverse expression pattern of NRG1 and ERBB3, suggesting HER3 activity in patients with significant tumor shrinkage in both arms.
B. Corresponding EGFR and NRG1 ligand co-expression associated with tumor shrinkage.
C. HPV(+) patients tended to have lower HER family ligand expression and no responses were seen in these patients.

Courtesy of A. Pirzkall, Oncology Biomarker development, Genentech

Penuel et al., AACR 2015
### Candidate Therapeutic Targets

#### Analysis – Tanguy Seiwort, Niki Schultz

<table>
<thead>
<tr>
<th>Receptor/Transcription/Kinase</th>
<th>HPV(-) N=244</th>
<th>HPV(+) N=35</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>16%</td>
<td>6%</td>
</tr>
<tr>
<td>FGFR1</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>MET</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>ERBB2</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>IGF1R</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>EPHA2</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>DDR2</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>FGFR2</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>FGFR3</td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td>CCND1</td>
<td>30%</td>
<td>3%</td>
</tr>
<tr>
<td>MYC</td>
<td>14%</td>
<td>3%</td>
</tr>
<tr>
<td>HRAS</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>18%</td>
<td>17%</td>
</tr>
<tr>
<td>PTEN</td>
<td>31%</td>
<td>10%</td>
</tr>
<tr>
<td>PIK3R1</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>NF1</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td>TP53</td>
<td>82%</td>
<td>3%</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>69%</td>
<td>9%</td>
</tr>
</tbody>
</table>

**Legend:**
- **Amplification**
- **Homozygous Deletion**
- **Heterozygous Deletion**
- **mRNA Downregulation**
- **Mutation**
- **RPPA Downregulation**
- **RPPA Upregulation**

*The Cancer Genome Atlas*

[TSeiwort_Draft_5/26/2013]
BERIL-1: A Phase II, Randomized, Placebo-controlled Study of Buparlisib and Paclitaxel in Platinum-pretreated Advanced SCCHN

Recurrent or metastatic SCCHN
Failure of one prior platinum-based therapy

Randomization (1:1)
Stratification by prior lines of treatment (1 vs 2) and study site (North America vs rest of world)

Buparlisib (100 mg/day) + paclitaxel (80 mg/m²/week)
Placebo + paclitaxel (80 mg/m²/week)

Primary endpoint
- PFS (local assessment, RECIST v1.1)

Key secondary endpoint
- OS

Secondary endpoints
- ORR, DCR, DoR
- Safety/tolerability
- Pharmacokinetics
- HRQoL

Exploratory biomarker assessments
- PI3K pathway activation status
- HPV status
- Molecular alterations in ctDNA/tumor tissue

Soulières D et al. Lancet Oncology 2017
Protocol-specified criteria for success were: HR ≤0.67 and posterior probability of (HR < 1) > 97.5%.

**BERIL-1 Primary Endpoint: Progression-free Survival**

- **6-month PFS rate:** 34% vs 19%
- **Buparlisib (n=79):** Median PFS, months = 4.6, Hazard Ratio (95% CI)* = 0.65 (0.45–0.95), One-sided p-value† = 0.011
- **Placebo (n=79):** Median PFS, months = 3.5

*The 97.5% Bayesian posterior probability criteria is equivalent to a 95% CI being <1; †Nominal p-value, not adjusted for multiple testing.

Soulières D et al. ASCO 2016:Abstract 6008
BERIL-1 Key Secondary Endpoint: Overall Survival

**BERIL-1 Key Secondary Endpoint: Overall Survival**

<table>
<thead>
<tr>
<th></th>
<th>Median OS, months</th>
<th>Hazard Ratio (80% CI)*</th>
<th>One-sided p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buparlisib (n=79)</td>
<td>10.4</td>
<td>0.72 (0.56–0.92)</td>
<td>0.041</td>
</tr>
<tr>
<td>Placebo (n=79)</td>
<td>6.5</td>
<td>(95% CI: 0.49–1.04)</td>
<td></td>
</tr>
</tbody>
</table>

Protocol-specified criteria for success were: HR ≤0.77 and posterior probability of (HR <1) >90.0%

12-month OS rate: 43% vs 33%

Number of patients at risk

- **Buparlisib**: 79, 67, 60, 54, 44, 39, 26, 20, 12, 7, 6, 2, 1, 1, 0
- **Placebo**: 79, 68, 55, 40, 30, 25, 21, 14, 10, 7, 4, 3, 3, 1, 0

*The 90% Bayesian posterior probability criteria is equivalent to a 80% CI being <1; †Nominal p-value, not adjusted for multiple testing.

Soulières D et al. Lancet Oncology 2017
• Diagnosis
• Prognosis
• Lung metastases: surgery?
• Re-irradiation and salvage surgery
• Chemotherapy
• Molecular biology and targeted therapies
• **Immunotherapy**
The role of immune checkpoint pathways in the immune response

TCR = T-cell receptor; PD-L1 = programmed death-ligand 1.
Overall survival


No separation in curves for first 3 months

BUT… Separation and survival impact occurs after 3 months – and median OS is increased

AND

Survival plateau after 2 years and we start to see long-term survivors

OS = overall survival.

Toxicity with Immuno-Oncology agents

- Activation of the immune system against tumors can result in a novel spectrum of Adverse events

AEs occur in certain organ systems:
- Skin
- Endocrine system
- Liver
- Gastrointestinal tract
- Nervous system
- Eyes
- Respiratory system
- Hematopoietic cells

- Can be serious
- Requires prompt recognition and treatment
- Requires patient and health care professional education
Patient with diarrhea
Patient with dyspnea
CheckMate 141 Study Design

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

Key Eligibility Criteria
- R/M SCCHN of the oral cavity, pharynx, or larynx
- Not amenable to curative therapy
- Progression on or within 6 months of last dose of platinum-based therapy
- ECOG PS 0–1
- Documentation of p16 to determine HPV status
- No active CNS metastases

Stratification factor
- Prior cetuximab treatment

Primary endpoint
- OS

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

Nivolumab
- 3 mg/kg IV q2w

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

CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papillomavirus; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomized; R/M, recurrent/metastatic; SCCHN, squamous cell carcinoma of the head and neck; Clinicaltrials.gov. NCT02105636.
Overall survival

<table>
<thead>
<tr>
<th></th>
<th>Median OS, mo (95% CI)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (n = 240)</td>
<td>7.7 (5.7, 8.8)</td>
<td>0.71</td>
<td>0.0048</td>
</tr>
<tr>
<td>Investigator’s choice (n = 121)</td>
<td>5.1 (4.0, 6.2)</td>
<td>(0.55, 0.90)</td>
<td></td>
</tr>
</tbody>
</table>

Gillison & Ferris ASCO 2017
# Treatment-Related AEs in ≥ 10% of Patients

<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&lt;sup&gt;a&lt;/sup&gt;</td>
<td>139 (58.9)</td>
<td>31 (13.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33 (14.0)</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (8.5)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (6.8)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>12 (5.1)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>10 (4.2)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>3 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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

Select AEs: AEs with potential immunologic etiology that requires monitoring/intervention
Phase 3 Keynote 040 study design

N=495

Pembrolizumab
200 mg IV Q3W for 2 y

Methotrexate 40 mg/m² QW
OR
Docetaxel 75 mg/m² Q3W
OR
Cetuximab 250 mg/m² QW

Key Eligibility Criteria
- SCC of the oral cavity, pharynx, or larynx
- PD after platinum-containing regimen
- ECOG PS 0 or 1

R 1:1

PRIMARY ENDPOINT: Overall survival

Cohen et al. LBA45
Overall survival (IIT population)

<table>
<thead>
<tr>
<th></th>
<th>Median OS, mo (95% CI)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>8.4 (6.4-9.4)</td>
<td>0.81 (0.66-0.99)</td>
<td>0.0204</td>
</tr>
<tr>
<td>SOC</td>
<td>7.1 (5.9, 8.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cohen et al. LBA45
Overall survival by PD-L1 expression

**PD-L1 CPS ≥1**

<table>
<thead>
<tr>
<th>Events, n</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>137</td>
<td>0.75a</td>
</tr>
<tr>
<td>SOC</td>
<td>157</td>
<td>(0.59-0.95)</td>
</tr>
</tbody>
</table>

Median (95% CI)

- 40.1% 26.7%
- 8.7 mo (6.9-11.4)
- 7.1 mo (5.7-8.6)

**PD-L1 TPS ≥50%**

<table>
<thead>
<tr>
<th>Events, n</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>41</td>
<td>0.54a</td>
</tr>
<tr>
<td>SOC</td>
<td>55</td>
<td>(0.35-0.82)</td>
</tr>
</tbody>
</table>

Median (95% CI)

- 46.6% 25.8%
- 11.6 mo (8.3-19.5)
- 7.9 mo (4.8-9.3)
Recurrent disease: **diagnosis**

- Pathology
- HPV

Amenable to curative treatment

- Surgery: lung nodules
- (Re)-Irradiation
- Local salvage surgery

Systemic treatment

- Symptoms
- Disease burden
- Comorbidities and PS
- Prognosis (HPV)
- Patient wishes

Best supportive care

Best supportive care Systemic treatment

PS 0-1

- Platin/5-FU/cetuximab
- Clinical trial

PS 2

Monotherapy
• Median survival of patients is 10-12 months (? Immunotherapy)

• First-line: Cisplatin /5-FU/cetuximab: standard of care

• Second-line: nivolumab or pembrolizumab

• Options: Platin/paclitaxel, taxanes, methotrexate
Recurrent SCCHN: first-line

Patients:
- Recurrent or metastatic HNSCC incurable by local therapies
- No prior systemic therapy for recurrent/metastatic disease
- Primary tumor locations of oropharynx, oral cavity, hypopharynx, or larynx (no nasopharynx)
- ECOG PS 0-1
- Able to provide tissue for PD-L1 biomarker analysis from a core or excisional biopsy
- HPV results available for oropharyngeal cancer

Randomization
1:1:1
N=780

- Pembrolizumab 200 mg Day 1 Q3W x 24 months
- Pembrolizumab (as above) + platinum + 5-FU Q3W x 6 cycles
- Cetuximab 250 mg/m² weekly (until PD/toxicity) + platinum + 5-FU Q3W x 6 cycles

Primary endpoint: progression-free survival
Nivolumab + ipilimumab in head and neck

Phase 3, randomized study

Patients with recurrent/metastatic SCCHN
• Tumor sample must be available for analysis of PD-L1 and HPV (oropharynx only)
• ECOG PS 0-1

Nivolumab + ipilimumab

Extreme regimen
Chemoradiation +/- Anti-PD1/PD-L1

Chemoradiation

Stage III/IV SCCHN

Chemoradiation +/- Anti-PD1/PD-L1
Courtesy of S. Lucas.
Immunosuppressive mechanisms

T-cell-intrinsic mechanisms
  CTLA-4/B7
  PD-1/PD-L1

Suppression by tumor cells
  PD-L1, FasL
  Depletion in tryptophane (IDO, ...)
  Secretion of immunosuppresive factor (TGF beta, ...)

Suppression by other cells
  Regulatory T cells (Tregs)
  Myeloid-derived suppressive cells (MDSCs)
  Tumor associated macrophages (TAMs)

Courtesy of S. Lucas
## Nivolumab + Epacadostat

<table>
<thead>
<tr>
<th>Patients, n(%)</th>
<th>Total (n=31)</th>
<th>Epacadostat 100 mg BID (n=7)</th>
<th>Epacadostat 300 mg BID (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>7 (23%)</td>
<td>1 (14%)</td>
<td>6 (25%)</td>
</tr>
<tr>
<td>CR</td>
<td>1 (3%)</td>
<td>0</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>PR</td>
<td>6 (19%)</td>
<td>1 (14%)</td>
<td>5 (21%)</td>
</tr>
<tr>
<td>SD</td>
<td>12 (39%)</td>
<td>1 (14%)</td>
<td>11 (46%)</td>
</tr>
<tr>
<td>PD</td>
<td>8 (26%)</td>
<td>4 (57%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>4 (13%)</td>
<td>1 (14%)</td>
<td>3 (13%)</td>
</tr>
</tbody>
</table>

Perrez et al. ASCO 2017