State of the Art: Management of Squamous Cell Carcinoma of the Head and Neck

Raul Giglio
Disclosures

• Nothing to disclose
SCCHN Outline

1. General considerations: MTD
2. Epidemiology
3. Locoregional disease
   1) Oral cavity
   2) Larynx and hypopharynx
   3) Oropharynx
4. R/M disease
Multidisciplinary decision

Validated options

Clinical trials
Introduction

- Head and neck cancer is the sixth most common type of cancer in the world

- Its incidence is on the rise (Oropharyngeal cancer)

- 600,000 new people are diagnosed every year with head and neck cancer, and 350,000 die from this disease

- Despite major advances in the treatment of head and neck cancer over the past decades, patient outcomes remain disappointingly unchanged

- Earlier diagnosis and referral to specialised healthcare professionals can have a major impact on improving the outcomes for head and neck cancer patients

- Current estimates indicate a 5-year survival rate of only 44% as a whole. But it is 80%-90% for head and neck cancer patients treated in the early stages of the disease
Head and Neck Cancer — Relative Frequencies in Different Regions

- Nasal sinuses (4%)
- Oral cavity (55%)
- Larynx (20%)
- Nasopharynx (1%)
- Oropharynx (15%)
- Hypopharynx (5%)

90% of cancers are found in:

- Oral cavity
- Larynx
- Oropharynx

Most are accessible on an oral physical exam!!!!

DeConti 1999.
### HPV-Positive vs HPV-Negative SCCHN

<table>
<thead>
<tr>
<th></th>
<th>HPV-Positive</th>
<th>HPV-Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anatomic site</strong></td>
<td>Tonsil/base of tongue</td>
<td>All sites</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Basaloid</td>
<td>Keratinised</td>
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<tr>
<td><strong>Age</strong></td>
<td>Younger</td>
<td>Older</td>
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<tr>
<td><strong>Gender</strong></td>
<td>3:1 men</td>
<td>3:1 men</td>
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<td><strong>SE status</strong></td>
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<td>Low</td>
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<td><strong>Risk factors</strong></td>
<td>Sexual behaviour</td>
<td>ETOH/tobacco</td>
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<tr>
<td><strong>Cofactors</strong></td>
<td>Marijuana/?immune suppression</td>
<td>ETOH/tobacco</td>
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<tr>
<td><strong>Incidence</strong></td>
<td>Rising</td>
<td>Declining</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td>Improved</td>
<td>Worse</td>
</tr>
</tbody>
</table>
HPV: Carcinogenesis

The p53 and pRB Pathways

- E6-AP
- HPV E6
- p53
- bax → Apoptosis
- p21cip1
- HPV E7
- cyclin/cdk
- p16
- ppRb
- pRB-E2F → Growth Arrest
Goals of Treatment of SCCHN

• Cure the patient
• Good functional results
• Minimise adverse events
• Early diagnosis of relapses and second primaries
• Reduce the long-term toxicity
• Ensure a good quality of life
• Allow the return to routine tasks
Issues in the Treatment of Tumours of SCCHN in 2016

- Personal characteristics of patients
- Comorbidities
- Natural history of each disease
- Different tumour sites require a particular and correct staging, treatment, and follow-up planning
- The modalities of treatment include surgery, radiotherapy, and chemotherapy in the majority of advanced tumours
Issues in the Treatment of Tumours of SCCHN in 2016

• Management of acute and chronic toxicities (education, care, and treatment)

• Need of suitable professional resources and continued medical education (preparation of guidelines)

• Establishment of multidisciplinary teams

• Participation and development of clinical and basic science trials
SCCHN: Tumour Issues to Consider

1. Site: oral cavity, oropharynx, larynx, hypopharynx, nasopharynx

2. Extension:
   1) Locoregional disease:
      i. Early stage (T1-2, N0; stage I/II)
      ii. Intermediate stage (stage III)
      iii. Advanced and resectable disease (stage IVa)
      iv. Inoperable advanced disease (stage IVb)
   2) Recurrent disease
      i. Resectable
      ii. Unresectable
   3) Metastatic disease

3. Treatment modalities:
   1) Single-modality treatment
   2) Combined-modality treatment

4. Biologic and epidemiologic differences
   1) Tobacco and alcohol
   2) HPV
   3) EBV
Early-Stage SCCHN
SCCHN: Early Stage

1. 30% or less of SCCHN

2. Single-modality treatment is the standard of care

3. Sites:
   1) Oral cavity: surgery (primary + SOH ND)\textsuperscript{a}
   2) Larynx and hypopharynx: surgery: TORS or laser\textsuperscript{a} radiotherapy
   3) Oropharynx: surgery: TORS or laser\textsuperscript{a} radiotherapy
   4) Nasopharynx: radiotherapy

\textsuperscript{a}Adjuvant RT or RT/CT according to pathology report.
Oral Cavity (Stages III and IVa)

• Surgery is the standard of care for fitted patients

• Adjuvant treatment with radiation is necessary in patients with adverse histologic features:
  – 2 or more positive lymph nodes
  – Histologic grade III
  – Perineural invasion
  – Intravascular invasion

• Adjuvant treatment with chemoradiation (HD cisplatin) is mandatory in patients in EORTC 22931 – RTOG 9501:
  – Positive margins
  – Extracapsular extension
OCAT: Conventional RT, Concurrent RT/CT, or Accelerated RT After Surgery in Locally Advanced Oral Cavity SCC\textsuperscript{1,2}

- Randomised phase III trial in locally advanced stage III/IV resectable SCC of the oral cavity
  - Arm A: surgery + conventional RT (56-60 Gy, 5 fractions/week)
  - Arm B: surgery + concurrent RT/CT (cisplatin 30 mg/m\textsuperscript{2} weekly; 56-60 Gy, 5 fractions/week)
  - Arm C: surgery + accelerated RT (56-60 Gy, 6 fractions/week)

- Results in brief
  - Concurrent CT or accelerated RT did not improve disease outcomes
  - The 5-year LRC for arms A and B was 59.9\% and 65.1\% (arm B vs arm A: $P = 0.203$; HR, 0.83; 95\% CI, 0.63-1.10) and 58.2\% for arm C (arm C vs arm A: $P = 1.02$; HR, 1.02; 95\% CI, 0.78-1.30)

\textsuperscript{1} Laskar SG et al. \textit{J Clin Oncol}. 2016;34:abstract 6004; \textsuperscript{2} Laskar SG et al. 2016 ASCO Annual Meeting.
Phase II Trial on Post-Surgery CT/RT in Combination With Cetuximab in SCCHN With High Risk of Locoregional Recurrence

• Results suggest that adjuvant RCT with concomitant and maintenance cetuximab is feasible and results in a favourable clinical outcome in high-risk SCCHN

• 2-year overall survival, disease-free survival, and locoregional tumour control rates were 86% (95% CI, 79%-95%), 77% (95% CI, 66%-86%), and 82% (95% CI, 93%-78%)

• A total of 1542 AEs, including 196 SAEs, were documented

RTOG 0920 Phase III Adjuvant Trial Intermediate-Risk Resected SCCHN

N = 700
S Resection

Intermediate risk
OC
LX
OF
T1 N1-2 M0
T2-4a N0-2 M0
Negative margins
No ECE

Primary Objective: OS
Secondary Objective: PFS

HPV (subanalysis) dysphagia, xerostomia, skin toxicity 12 and 24 m
Randomised Phase II/III Trial of Surgery and Postoperative Radiation Delivered With Concurrent Cisplatin vs Docetaxel vs Docetaxel and Cetuximab for High-Risk SSCHN (RTOG 1216)

Stratification
PS 0 vs 1

Tumour site:
- OC
- LX
- HF
- OF P16-negative

Expression of EGFR:
- High
- Low
- ND

IMRT (60 Gy/6 weeks) + CDDP
40 mg/m² weekly/6 doses

IMRT (60 Gy/6 weeks) + docetaxel
15 mg/m² weekly/6 doses

IMRT (60 Gy/6 weeks) + cetuximab
400 mg/m² followed by 250 mg/m² weeks + docetaxel 15 mg/m² weekly/6 doses
Concurrent Chemoradiotherapy (CRT)
Induction/Sequential CRT
Concurrent vs Induction/Sequential CRT
Concurrent Therapy: Standard of Care

- Concurrent administration of chemotherapy and radiotherapy is recommended in advanced SCCHN
- Survival benefit 10% over radiotherapy alone
- Acute grade 3-4 toxicity around 50% (may be less with IMRT)
- Late grade 3-4 toxicity (dysphagia) around 40%
- 10% not treatment-related deaths

- Typical regimen:
  - Cisplatin 100 mg/m² days 1, 22, and 43 of RT
  - RT standard fractionation, 70 Gy over 7 weeks (2-Gy fractions)

- Potential approaches to improve on CRT:
  - Addition of induction chemotherapy
  - Accelerated fractionation of RT (not better according to RTOG 0129)
Induction Therapy: Clinical Considerations

**Scenarios in Which to Consider Induction Therapy**

1. Potential distant metastasis
2. Delay in radiation simulation
3. Impending local issue (e.g., airway)
4. Markedly advanced disease (e.g., bulky, N2c, N2b, N3, low neck, dermal infiltration)
5. Organ preservation strategy in patients with markedly advanced disease

**Impact of Induction Chemotherapy (CT): Opposing Views and Ongoing Controversy**

**Pros**
- Allows time to optimise patient medical status
- Possible customisation of RT dosing based on response to treatment
- Provides early treatment of distant micrometastatic disease

**Cons**
- Induction CT may adversely affect compliance to subsequent concurrent CT/RT or choice of CT/RT regimen
- Adds 2-4 months to treatment
Larynx and Hypopharynx: Organ Preservation
RTOG 91-11

PF induction

No Response ➔ S + RT ➔ FU
Response ➔ RT ± salvage S

Concomitant RT-CT (cisplatin days 1, 22, and 43)

<table>
<thead>
<tr>
<th>TNM</th>
<th>Induction N = 173 (%)</th>
<th>Concomitant N = 172 (%)</th>
<th>RT Alone N = 173 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>11</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>T3</td>
<td>78</td>
<td>78</td>
<td>79</td>
</tr>
<tr>
<td>T4</td>
<td>10</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>N0</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>N1</td>
<td>22</td>
<td>23</td>
<td>18</td>
</tr>
</tbody>
</table>
RTOG-91-11 Ten-Year Update: Induction Cisplatin/5-FU + RT vs Concurrent Cisplatin + RT vs RT Alone in LX Preservation

A) Laryngeal Preservation (%)
   - RT + ind.
   - RT + conc.
   - RT only

B) Primary Endpoint LFS
   - Laryngectomy-Free Survival (%)

C) OS
   - Overall Survival (%)
   - RT + ind.
   - RT + conc.
   - RT only
   - 38.8%
   - 27.5%

D) Locoregional Control (%)
   - Time Since Random Assignment (years)

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Gortec 2000-2001: Larynx Preservation Trial
Results—10 Years of Follow-Up

Results
Larynx Preservation

Larynx DysFunction Free Survival

Survival rate (%)

Time to randomization (year)

p = 0.01

p = 0.001
• Phase III randomised trial in non-operated, non-metastatic \( \geq \text{N2b} \) stage III/IV SCCHN patients regardless of HPV status

• Results:
  
  – No PFS difference – 11.5 m (arm A) vs 12.5 m (arm B); HR, 0.95 (95% CI, 0.72-1.27; \( P = 0.74 \))
  
  – No OS difference – 24.6 m vs 22.8 m; HR, 1.10 (95% CI, 0.84-1.45)
  
  – Locoregional control similar between groups – 46.6% vs 43.3%; HR, 0.97 (95% CI, 0.84-1.45; \( P = 0.85 \))
  
  – Distant metastasis–free – 86.4% vs 92.9%; HR, 0.50 (95% CI, 0.22-1.11, \( P = 0.081 \))

• Conclusion: induction TPF then cetuximab/RT was not superior to concurrent CT/RT
Outcomes With CT/RT According to HPV Status

RTOG 0129 trial

TROG 02.02 trial
RTOG 0129 Trial Risk Stratification

Oropharyngeal cancer (n=266)

- HPV-positive
  - ≤10 pack-years (n = 88)
    - N0-N2a (n = 26)
      - 42.9% at low risk
        - 3-year OS = 93.0%
  - >10 pack-years (n = 90)
    - N2b-N3 (n = 64)
      - 29.7% at intermediate risk
        - 3-year OS = 70.8%

- HPV-negative
  - ≤10 pack-years (n = 23)
    - T2-T3 (n = 15)
      - 27.4% at high risk
        - 3-year OS = 46.2%
  - >10 pack-years (n = 65)
    - T4 (n = 8)

42.9% at low risk
3-year OS = 93.0%
27.4% at high risk
3-year OS = 46.2%
OF-HPV Is a Favourable Prognostic Factor Beyond Progression

A. Locoregional progression

B. Distant progression

C. With salvage S

D. No salvage S
How Can We Reduce Acute and Long-Term Toxicity?

• Locoregional control paradigm
  – Reduce the dose of RT prior to selection according to response to the QTNA (E1308)
  – Keep the ID RT without CT
  – Reduce the ID of RT with CT concomitantly
  – Reduce the ID of RT without CT

(Severe smokers may need more intensive treatments)

• MD control paradigm:
  – Use CT or other systemic treatments for MD and not just for locoregional treatment
  – Consider NACT: followed by CT/RT with reducing doses of RT (E1308)
  – Skip CT/RT in responders but keep the ID of RT
**Bioradiotherapy (BRT)**

Stage III and IV non-metastatic SCCHN \( (n = 424) \)

**Stratified by**
- KPS
- Nodal involvement
- Tumour stage
- RT regimen\(^a\)

RT \( (n = 213) \)

ERBITUX + RT \( (n = 211) \)
- ERBITUX initial dose (400 mg/m\(^2\))
- 1 week before RT
- ERBITUX (250 mg/m\(^2\)) + RT (weeks 2-8)

**Primary endpoint:** Duration of locoregional control

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

Erbitux in Locally Advanced SCCHN: 5-Year Survival Update

HR = 0.73 [95% CI: 0.56–0.95]  
*p = 0.018

Overall survival (%)

- RT
- Erbitux + RT

5-year survival rate
- 49.0 months (46%)
- 29.3 months (36%)

Bonner et al. Lancet Oncol 2010
SCCHN Comparison
(MACH-NC Meta-Analyses, Bonner Study)

Ongoing Clinical Trials
RTOG 1016: OF HPV+ (Nonresectable)

Stratification
- T
- N
- PS
- Smoking history
  - (T1N+, T2N1 are excluded)
- N = 1000

Primary endpoint: OS (noninferior)

RT HF
- 70Gy/35 Fx/6 weeks + Cisplatin 100 mg/m² q
  - 3 weeks × 2

RT HF
- 70 Gy/35 Fx/6 weeks + cetuximab 400 weeks × 1
  - cetuximab 250 mg/m² weekly
OPTIMA Trial (HN HPV+)

SCCHN locally advanced
HPV +
NACT (3 cycles)

Clinical, radiographic and pathologic evaluation

Low-risk pts
Excellent response
Single-therapy
(CT/RT low dose)

Intermediate-risk pts
intermediate response
CT/RT
(RT low dose)

High-risk pts
Poor response
CT/RT
(RT standard dose)
NRG HN002 Trial
Phase II of HPV+ or Nonsmokers

OF
- HPV+
- <10 p/y
- T1-T2 N1-N2b
- T3 N0-N2b

RT
- 60 Gy in 6 weeks (2 Gy/Fx) + weekly concomitant cisplatin 40 mg/m² × 6

RT alone
- 60 Gy in 5 weeks (2 Gy/Fx), 6 fractions per week
Recurrent and/or Metastatic SCCHN
R/M Head and Neck Cancer Patients (Not Suitable for Salvage Surgery or Re-irradiation)

- Cisplatin-sensitive patients:
  - Recurrence after combined-modality treatment with cisplatin with a PFS of more than 6 months
  - R/M disease in cisplatin-naive patients

- Cisplatin-refractory patients:
  - Recurrence after combined-modality treatment with cisplatin within 6 months
  - Progression after a first-line treatment with cisplatin for R/M disease
R/M SCCHN First-Line Treatment (Cisplatin-Sensitive)

- Combination doublets with cisplatin in patients with PS 0-1
- 30%-40% chance of response with platinum-fluorouracil (PF)
- Difficult to obtain response in irradiated areas (some patients have only stabilisation)
- The duration of the response is short
- The median survival is 6-7 months
- Response rate with cisplatin is 10% superior compared with carboplatin with any of their combinations
R/M First-Line Treatment in Cisplatin-Sensitive Patients

**EXTREME: Study design**

**Randomized**

**Group A**
- Either cisplatin (100 mg/m² IV, d1)
- Or carboplatin (AUC 5, d1)
- + 5-FU (1000 mg/m² IV, d1–4):
  - 3-week cycles
- + ERBITUX 400 mg/m² initial dose then 250 mg/m² weekly

**Group B**
- Either cisplatin (100 mg/m² IV, d1)
- Or carboplatin (AUC 5, d1)
- + 5-FU (1000 mg/m² IV, d1–4):
  - 3-week cycles

6 chemotherapy cycles maximum

**ERBITUX**

**No treatment**

**Progressive disease or unacceptable toxicity**

EXTREME Trial: Overall Survival

Survival probability

Survival time (months)

Patients at risk

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
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</thead>
<tbody>
<tr>
<td>CTX only</td>
<td>220</td>
<td>173</td>
<td>127</td>
<td>83</td>
<td>65</td>
<td>47</td>
<td>19</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>CTX + ERBITUX</td>
<td>222</td>
<td>184</td>
<td>153</td>
<td>118</td>
<td>82</td>
<td>57</td>
<td>30</td>
<td>15</td>
<td>3</td>
</tr>
</tbody>
</table>

HR [95%CI]: 0.80 [0.64–0.99]
p=0.04

7.4 months

10.1 months
EXTREME Trial: Conclusions

1. The addition of Erbitux to platinum-based chemotherapy with fluorouracil significantly extended overall survival by 2.7 months

2. It reduced the risk of disease progression by 46%

3. Response rate was increased by 83%

4. It did not modify the profile of adverse events

5. It did not have a negative impact on quality of life

6. The combination of platinum/carboplatin + fluorouracil + Erbitux is the first systemic treatment that has shown an increase in survival in more than 30 years
Cisplatin-Refractory R/M SCCHN

- There is no standard treatment
- Anticancer treatments have not increased survival
- Chemotherapy, monoclonal anti-EGFR and TKI anti-EGFR were tested in randomised trials
- Survival is very poor (≤6 months)
- Immunotherapy is a new treatment option in this setting
## Cisplatin-Refractory Patients With SCCHN: Randomised Trials

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>CONTROL</th>
<th>ORR</th>
<th>PFS</th>
<th>SV</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMEX</td>
<td>GEFITINIB 250 MG</td>
<td>2.7</td>
<td>NA</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td>GEFITINIB 500 MG</td>
<td>7.6</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>MTX</td>
<td>3.9</td>
<td>NA</td>
<td>6.7</td>
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<tr>
<td>ECOG 1302</td>
<td>D + PLACEBO</td>
<td>6</td>
<td>2.2</td>
<td>6.2</td>
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<tr>
<td></td>
<td>D + GEFITINIB</td>
<td>12</td>
<td>3.3</td>
<td>6.8</td>
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<td>ZALUTE</td>
<td>BSC + ZALUTUMUMAB</td>
<td>6</td>
<td>2.3</td>
<td>6.7</td>
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<tr>
<td></td>
<td>BSC ± MTX</td>
<td>1</td>
<td>1.9</td>
<td>5.2</td>
</tr>
</tbody>
</table>
Importance of ErbB Family Members in Metastatic SCCHN

- Most patients with SCCHN present with advanced disease (stage II and IV)\(^1\)
- EGFR overexpression is associated with poor tumour differentiation and advanced tumour stage, is upregulated in histologically normal tissue adjacent to the tumour, and is thought to provide a survival benefit to tumour cells during early metastasis\(^2\)
- Downstream effectors of EGFR have been implicated in SCCHN tumour metastasis\(^2\)
  - Increased levels of activated ERK1/2 are associated with advanced tumour stage and lymph node metastasis
  - Phospholipase C\(\gamma\)1 activation has been shown to promote SCCHN migration

Targeting of EGFR has had only modest success in SCCHN; only one mAb has shown success in clinical trials; all others have fallen short\(^1,2\)

The interplay between EGFR and the other ErbB family members may determine sensitivity or resistance to EGFR-targeted therapies\(^2\)

**EGFR (ErbB1)**
- >90% overexpression in SCCHN tumours²,³
- Increased gene expression and high levels of protein expression are associated with decreased survival, resistance to radiotherapy, locoregional treatment failure, and increased rates of distant metastases⁴-⁶

**HER2 (ErbB2)**
- Overexpression in SCCHN: 3%-29%⁷

**ErbB3**
- Overexpression in SCCHN: 21%⁷

**ErbB4**
- Overexpression in SCCHN: 26%⁷

- mAb EGFR-targeted therapy has been approved for the treatment of SCCHN⁸
- However, only a subset of SCCHN patients (regardless of EGFR overexpression) respond to currently available EGFR-targeted therapies, and patients often develop resistance⁹

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ErbB = proto-oncogene B of the avian erythroblastosis virus.

**LUX: HNC 1 (1200.43) Afatinib vs MTX in Second-Line R/M SCCHN**

<table>
<thead>
<tr>
<th>Trial Design</th>
<th>Endpoints</th>
<th>Study Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase III</strong>, randomised, open-label</td>
<td><strong>Primary: PFS</strong>&lt;br&gt;Key secondary: OS; HR 0.73</td>
<td>Global</td>
</tr>
</tbody>
</table>

**N = 483**

R/M SCCHN
- Failing platinum-based CT for R/M SCCHN
- Documented PD
- PS = 0-1
- Max 1 CT regimen for R/M SCCHN
- No prior EGFR TKIs

Afatinib 40 mg qd PO<br>N = 316

MTX 40 mg/m² qw IV<br>N = 158

Stratified by:<br>ECOG PS, previous EGFR-targeted mAb for recurrent or metastatic disease

**Let’s Work**

## LUX: HNC 1 (1200.43) Afatinib vs MTX in Second-Line R/M SCCHN – Efficacy

### Table

<table>
<thead>
<tr>
<th>Trial Design</th>
<th>Afatinib</th>
<th>Methotrexate</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N = 483)</td>
<td>(N = 332)</td>
<td>(N = 161)</td>
<td></td>
</tr>
<tr>
<td>Median PFS (primary EP)</td>
<td>2.6 months</td>
<td>1.7 months</td>
<td>0.03</td>
</tr>
<tr>
<td>Median OS</td>
<td>6.8 months</td>
<td>6 months</td>
<td>NS</td>
</tr>
<tr>
<td>Disease Control Rate</td>
<td>49.1%</td>
<td>38.5%</td>
<td>0.035</td>
</tr>
<tr>
<td>Overall Response Rate</td>
<td>10.2%</td>
<td>5.6%</td>
<td>0.10</td>
</tr>
</tbody>
</table>

LUX: HNC 1 (1200.43) Afatinib vs MTX in Second-Line R/M SCCHN – PFS


<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Afatinib (n = 322)</th>
<th>MTX (n = 161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS event, n (%)</td>
<td>275 (85.4)</td>
<td>135 (83.9)</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>2.6</td>
<td>1.7</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.80 (0.65-0.98)</td>
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</tr>
<tr>
<td>Log-rank test P value</td>
<td>0.030</td>
<td></td>
</tr>
</tbody>
</table>
Afatinib significantly improved PFS vs methotrexate

Tumour shrinkage was greater, response rate higher, and DCR significantly higher compared with methotrexate

Patient-reported outcomes favoured afatinib over methotrexate

OS was not significantly different between afatinib and methotrexate

Overall AE profiles were as expected
  - Fewer treatment-related dose reductions, discontinuations, and fatal events with afatinib compared with methotrexate

Afatinib has shown efficacy and improved patient-reported outcomes in a Phase III trial in this setting
Additional Targets for SCCHN
## Candidate Therapeutic Targets

<table>
<thead>
<tr>
<th>Genes</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>ERBB2</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>IGF1R</td>
<td>4%</td>
<td>3%</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>11%</td>
</tr>
<tr>
<td>MET</td>
<td>2%</td>
<td>0%</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>5%</td>
<td>0%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>18%</td>
<td>37%</td>
</tr>
<tr>
<td>PTEN</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>PIK3R1</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>NF1</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>TP53</td>
<td>83%</td>
<td>3%</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>58%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Legend:**
- Amplification
- Homozygous Deletion
- Mutation
- RPPA Downregulation
- RPPA Upregulation
- FGFR3-TACC3 Fusion
- EGFR VIII
- MET Exon 14 Skipping

TCGA. Nature. 2015.
Immunotherapy in SCCHN
KEYNOTE-012 – Phase Ib Study of Pembrolizumab in Patients With R/M HNSCC: Pooled Analysis After Long-Term Follow-up

Study Design

- **Patients**
  - R/M HNSCC
  - Measurable disease (RECIST v1.1)
  - ECOG PS 0-1
  - PD-L1+ (initial cohort)
  - PD-L1+ or PD-L1- (expansion cohort)

- **Initial Cohort**
  - Pembrolizumab 10 mg/kg Q2W
  - $N = 60$

- **Expansion Cohort**
  - Pembrolizumab 200 mg Q3W
  - $N = 132$

- **Continue until**
  - 24 months of treatment
  - PD
  - Intolerable toxicity

- **Combined analyses of Initial and Expansion cohorts**

**Response assessment:** Every 8 weeks

**Primary end points:** ORR (RECIST v1.1, central imaging vendor), safety

**Secondary end points:** ORR (investigator), PFS, OS, response duration, ORR in HPV+ patients

Pembrolizumab (Keytruda) was approved in August 2016 by the FDA for R/M SCCHN progressed on platinum-based therapy, based on this study.

Mehra et al. 2016 ASCO Annual Meeting.
## KEYNOTE-012: Best Overall Response

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>Total N = 192&lt;sup&gt;†&lt;/sup&gt;</th>
<th>HPV+ n = 45&lt;sup&gt;‡&lt;/sup&gt;</th>
<th>HPV− n = 147&lt;sup&gt;‡&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>ORR</td>
<td>34</td>
<td>18</td>
<td>13–24</td>
</tr>
<tr>
<td>CR</td>
<td>8</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>PR</td>
<td>26</td>
<td>14</td>
<td>–</td>
</tr>
<tr>
<td>SD</td>
<td>33</td>
<td>17</td>
<td>–</td>
</tr>
<tr>
<td>PD</td>
<td>93</td>
<td>48</td>
<td>–</td>
</tr>
<tr>
<td>NA§</td>
<td>32</td>
<td>17</td>
<td>–</td>
</tr>
</tbody>
</table>
KEYNOTE-012 – Change of Tumour Size From Baseline

60% of patients had a decrease in target lesions.

-20% increase
-30% decrease

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>Total N = 192†</th>
<th>HPV+ n = 45‡</th>
<th>HPV− n = 147‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>95% CI</td>
<td>n</td>
</tr>
<tr>
<td>ORR</td>
<td>34</td>
<td>18</td>
<td>13–24</td>
</tr>
</tbody>
</table>

### KEYNOTE-012: Best Overall Response

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>Total N = 192†</th>
<th>HPV+ n = 45‡</th>
<th>HPV− n = 147‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>ORR</td>
<td>34</td>
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</tr>
<tr>
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<td>4</td>
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<td>14</td>
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</tr>
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</tr>
<tr>
<td>NA§</td>
<td>32</td>
<td>17</td>
<td>–</td>
</tr>
</tbody>
</table>

† Numbers may not add up to the total due to rounding.  
‡ Numbers may not add up to the total due to rounding.

KEYNOTE-055 – Pembrolizumab After Platinum and Cetuximab Failure in HNSCC: Study Design

Patients
- Recurrent/metastatic HNSCC
- Resistant to platinum and cetuximab†
- Measurable disease (RECIST v1.1)
- ECOG PS 0-1

Pembrolizumab 200 mg Q3W Flat Dose

Continue until:
- 24 months of treatment
- PD
- Intolerable toxicity
- Investigator/patient decision

Safety and Survival Follow-up

Response assessment: Every 6-9 weeks
Primary end points: ORR (RECIST v1.1, central imaging vendor) in all patients and PD-L1+ patients, safety
Secondary end points: ORR in HPV+ patients, PFS, OS, duration of response

KEYNOTE-055 – Pembrolizumab After Platinum and Cetuximab Failure in HNSCC: Results

54% had a decrease in target lesions

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>Patients With ≥6 Months Follow-up n = 92</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>ORR†</td>
<td>16</td>
</tr>
<tr>
<td>PR</td>
<td>16</td>
</tr>
<tr>
<td>SD</td>
<td>17</td>
</tr>
<tr>
<td>PD</td>
<td>51</td>
</tr>
<tr>
<td>NA‡</td>
<td>8</td>
</tr>
</tbody>
</table>

Checkmate 141 – Nivolumab vs Investigator’s Choice Chemotherapy in R/M HNSCC After Platinum Therapy

<table>
<thead>
<tr>
<th>Trial Design</th>
<th>Endpoints</th>
<th>Study Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III, Open-label, randomised</td>
<td>Primary: PFS, OS Secondary: ORR</td>
<td>Global</td>
</tr>
</tbody>
</table>

R/M SCCHN
- PS = 0-1
- Progression within 6 months of last platinum chemotherapy

N = 180

Nivolumab 3 mg/kg IV q 2 weeks until PD
Cetuximab or MTX or docetaxel until PD

Nivolumab (Opdivo) currently has FDA breakthrough and priority review status for SCCHN. Based on the interim results of Checkmate 141, marketing applications for Opdivo in R/M SCCHN have been accepted by the FDA and EMA. Projected action date: November 2016.

Please see notes for reference list.
Checkmate 141 – Nivolumab vs Investigator’s Choice Chemotherapy in R/M HNSCC: Interim Results


<table>
<thead>
<tr>
<th>Treatment</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>0.51 (0.96)</td>
<td></td>
</tr>
</tbody>
</table>

1-year OS rate (95% CI)

- Nivolumab: 36.0% (28.5, 43.4)
- Investigator’s Choice: 16.6% (8.6, 26.8)
### Checkmate 141 – Nivolumab vs Investigator’s Choice Chemotherapy in R/M HNSCC: Interim Results

<table>
<thead>
<tr>
<th>Objective response rate, n (%)</th>
<th>Nivolumab (n = 240)</th>
<th>Investigator’s Choice (n = 121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate, n (%)</td>
<td>32 (13.3)</td>
<td>7 (5.8)</td>
</tr>
<tr>
<td>95% CI</td>
<td>9.3, 18.3</td>
<td>2.4, 11.6</td>
</tr>
</tbody>
</table>

**Best overall response, n (%):**

<table>
<thead>
<tr>
<th>Response</th>
<th>Nivolumab (n = 240)</th>
<th>Investigator’s Choice (n = 121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>6 (2.5)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Partial response</td>
<td>26 (10.8)</td>
<td>6 (5.0)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>55 (22.9)</td>
<td>43 (35.5)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>100 (41.7)</td>
<td>42 (34.7)</td>
</tr>
<tr>
<td>Not determined</td>
<td>53 (22.1)</td>
<td>29 (24.0)</td>
</tr>
</tbody>
</table>

**Time to response, mo**

<table>
<thead>
<tr>
<th>Median (range)</th>
<th>Nivolumab (n = 240)</th>
<th>Investigator’s Choice (n = 121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range)</td>
<td>2.1 (1.8–7.4)</td>
<td>2.0 (1.9–4.6)</td>
</tr>
</tbody>
</table>
# Conclusions

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

- Nivolumab is the first agent to demonstrate a significant improvement in survival in patients with SCCHN who progress after platinum-based therapy in a global, phase 3 comparative trial.
  - Nivolumab doubled the 1-year survival rate: 36% with nivolumab compared to 17% for investigator’s choice therapy.
- Nivolumab demonstrated a survival benefit in the overall study population regardless of PD-L1 expression or p16 status.
- Magnitude of OS benefit of nivolumab vs investigator’s choice was greater in patients expressing PD-L1, and increasing PD-L1 expression did not result in further benefit.
- There were fewer treatment-related adverse events with nivolumab vs investigator’s choice therapy.
- Nivolumab stabilized PROs while investigator’s choice led to meaningful declines in function and worsening of symptoms.
- Nivolumab is a new standard-of-care option for patients with R/M SCCHN after platinum-based therapy.

Ongoing Trials With Immunotherapy

Platinum-Refractory Patients
Keynote 040 Trial

**Primary endpoint**: OS
**Secondary endpoints**: PFS, response, safety biomarkers, QOL

**Inclusion criteria**
- R/M SCCHN CO, OF, HF and LX
- Progression to CDDP within 6 months
- Unlimited treatment lines
- P16 documented for OF regardless of PD-L1 stratification:
  - PS
  - HPV
  - Smoking status

**Pembrolizumab**
- 200 mg C/3 weeks

**Investigator choice**
- MTX 40 mg/m² IV weekly
- DTX 30 mg/m² IV weekly
- Cetuximab 400 mg/m² followed by 250 mg/m² weekly
EAGLE Trial

**Primary objective:** Survival

**Secondary objectives:** PFS, response, safety biomarkers, QOL

**Inclusion criteria**
- R/M SCCHN CO, OF, HF and LX
- PD within 6 months after cisplatin
- No treatment lines limit
- P16 documented for OF
- Independent of PD-L1 stratification:
  - PS
  - HPV status
  - Smoking status

**Investigator choice**
- Durvalumab
- Durvalumab + tremelimumab
- MTX 40 mg/m² IV weekly
- DTX 30 mg/m² IV weekly
- Cetuximab 400 mg/m² followed by 250 mg/m² weekly
Ongoing Trials in Immunotherapy
Platinum-Sensitive Patients
Combination Immunotherapy: KESTREL – Durvalumab ± Tremelimumab vs Standard of Care in R/M SCCHN

- Phase III, randomised, open-label study of first-line durvalumab ± tremelimumab vs standard of care (EXTREME regimen) in R/M SCCHN

Seiwert TY et al. 2016 ASCO Annual Meeting.
Keynote 048 Trial

Inclusion criteria
R/M SCCHN CO, OF, HF and LX
Progression ≥6 months after locoregional combined treatment with platinum
Platinum-naive

Primary objective: PFS (RECIST criteria)
Secondary objectives: PFS (investigator), OS, response
Checkmate 651 Trial

Primary objective: survival and PFS

Inclusion criteria:
R/M SCCHN CO, OF, HF and LX
Progression ≥6 months after locoregional combined treatment with platinum
Platinum-naive

Nivolumab + ipilimumab
Cetuximab 400 mg/m² followed by 250 mg/m² weekly
CDDP or CBDCA + FU
Maintenance with CTX
Conclusions: Treatment of SCCHN in 2016

- Multiple options available
  - Concurrent CT/RT
  - Sequential therapy: TPF is the standard induction regimen
  - Targeted therapy: cetuximab/RT

- Patient selection is important
  - Stage, patient characteristics, PS, and primary site

- HPV-related oropharynx disease is a major public health problem
  - HPV-positive and HPV-negative disease are distinct entities
    - Pts with HPV-positive disease demonstrate improved responses to therapy and better survival
    - De-intensification is a relevant research question
Thank You!
Questions?