Recent Advances & Ongoing Challenges in Head & Neck Cancers

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Disclosures

- Research Funding: BMS, Merck, Pfizer, Celgene, Astra Zeneca, Genentech
- Consultant: Merck, BMS, Eisai, Pfizer, Astra Zeneca, Genentech, Loxo
- NCCN: Member: Head and Neck Committee
- NCCN: Chair: Thyroid Committee
Head and Neck Cancer

• Introduction:
  Epidemiology, Clinical Features, Prevention, Treatment Modalities

• Concurrent Chemoradiotherapy

• Sequential Chemoradiotherapy

• Adjuvant Chemoradiotherapy

• Recurrent/Metastatic disease
Head and Neck Cancer Primary Disease Sites

- Oral Cavity
- Pharynx
- Larynx
- Nasal Cavity
- Paranasal Sinuses

Source: Maxwell V. Blum Cancer Resource Room
Epidemiology

- 48000 new cases per year in US.
- Median age of diagnosis: ~60 years
- Male>Female
- Strongly associated with tobacco and alcohol
- Epstein-Barr virus risk factor for nasopharynx cancers
- Human papillomavirus increasingly appreciated as a risk factor
Human Papillomavirus (HPV)

HPV-Associated Cancers

> 99% of Cervical Carcinoma
  ~ 90% Anal Carcinomas
  ~ 40% Vulvar and Vaginal Carcinomas
  ~ 60% of Oropharynx Cancers

HPV GENOME INTEGRATION

Frequent Event During Malignant Progression
Terminates Viral Life Cycle
Expression of E6 and E7 Is Retained

HPV E6/E7 Oncoproteins

Small, Non-Enzymatic Proteins
(~ 150aa E6; ~ 100aa E7)
Associate With and Functionally Modify
Host Cellular Protein Complexes

Circular 8 kB dsDNA Genomes
Only One Coding Strand
Infect Epithelial Cells
~ 200 HPV types
~ 30 Mucosal HPVs
Low-Risk: Genital Warts
High-Risk: Lesions That Progress to Cancer
Human Papillomavirus (HPV)-Positive Head and Neck Cancer

- HPV 16 is the viral subtype in the vast majority of patients.
- Half of oropharynx cancers will have HPV 16 DNA.
- Often occurs in nonsmokers, nondrinkers.
- Median age younger than HPV-negative patients; incidence increasing.
- Associated with ↑ number of sexual partners and high-risk sexual practices.
- Favorable prognosis.
- In situ hybridization, p16 IHC, PCR.

Rising Incidence of HPV-Associated Cancers

Survival Outcomes by HPV Status in Oropharyngeal Cancer in RTOG 0129

Ang et al NEJM 2010
RTOG 0129 Phase III Trial: Concomitant CRT With Standard Vs. Accelerated Fractionation RT

Stage III/IV (T2, N2–3, M0, or T3–4, any N, M0) SCCHN
- Oral cavity, oropharynx, hypopharynx, larynx
- No prior RT to head and neck except radioactive iodine therapy
- No prior surgery to primary tumor or nodes except for diagnostic biopsy

Expected N = 720

Cisplatin (IV on D1, 22, 43)
Standard fractionation RT (5 d/wk for 7 wks)

Cisplatin (IV on D1, 22)
Accelerated fractionation RT (5 d/wk for 3.5 wks; then twice daily, 5 d/wk for 2.5 wks)
RTOG 0129: OS and PFS by HPV Status

3-Year Outcomes | HPV Positive (%) | HPV Negative (%) | P Value
---|---|---|---
OS | 82.4 | 57.1 | <0.001
PFS | 73.7 | 43.4 | <0.001
Locoregional failure | 13.6 | 35.1 | <0.001
Distant metastases | 8.7 | 14.6 | 0.23

HR=0.38 (95% CI:0.26-0.55); P<0.001
HR=0.40 (95% CI:0.29-0.557; P<0.001

Two distinct HNSCC entities

<table>
<thead>
<tr>
<th></th>
<th>HPV positive</th>
<th>HPV negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomic site</td>
<td>Tonsil /Base of Tongue</td>
<td>All sites</td>
</tr>
<tr>
<td>Histology</td>
<td>Basaloid</td>
<td>Keratinized</td>
</tr>
<tr>
<td>Age</td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td>Gender</td>
<td>3:1 men</td>
<td>3:1 men</td>
</tr>
<tr>
<td>SE status</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Sexual behavior</td>
<td>ETOH/tobacco</td>
</tr>
<tr>
<td>Cofactors</td>
<td>Marijuana/?immune suppression</td>
<td>ETOH/tobacco</td>
</tr>
<tr>
<td>Incidence</td>
<td>Rising</td>
<td>Declining</td>
</tr>
<tr>
<td>Survival</td>
<td>Improved</td>
<td>Worse</td>
</tr>
</tbody>
</table>

There is a major change in the etiology of head and neck cancer, the incidence of OPC rapidly increasing mostly in North America and Europe. Should we treat them the same?
E1308: Phase II Trial of Induction Chemotherapy Followed by Reduced-Dose Radiation and Weekly Cetuximab in Patients With HPV-Associated Resectable Squamous Cell Carcinoma of the Oropharynx—ECOG-ACRIN Cancer Research Group

Marur et al: JCO 2016
ECOG 1308: Phase II Schema

**Induction Chemotherapy**
- **Cisplatin** 75mg/m² d1
- **Paclitaxel** 90mg/m² d1,8,15
- **Cetuximab** 250mg/m² d1,8,15
- Q 21 days for 3 cycles

**Concurrent Chemoradiation**
- **CLINICAL CR**
  - Low dose IMRT 54Gy/27fx* + Cetuximab qWeek
- **CLINICAL PR/SD**
  - Full dose IMRT 69.3Gy/33fx* + Cetuximab qWeek

**Eligibility**
- Oropharynx SCC
- HPV ISH + and / or p16+
- Stage III, IVA

*Marur et al: JCO 2016*
PFS (A) and OS (B) in cohort with clinical complete response to induction chemotherapy treated with low-dose radiation of 54 Gy (n = 51).
PFS (A) and OS (B) in favorable cohort (non-T4, non-N2c, ≤ 10 pack-year smokers) with clinical complete response to induction chemotherapy treated with low-dose radiation of 54 Gy (n = 27).
• Induction chemo followed by reduced-dose IMRT/Cetuximab was feasible in a Cooperative Group setting

• CCR to induction was noted in 70% (56/80), and was well tolerated.

• The 2yr PFS in 54Gy IMRT patients was 80% (95% CI 0.70, 0.88) and 2yr OS was 94%.

• Best results of 54Gy was in smokers <10pk-yrs, non T-4 and non-N2c: 2yr PFS and 2yr OS of 96% (n=27)

• At 12 months: fewer pts in low dose had difficulty with swallowing solids.

• This approach remains investigational. Further studies are planned
## Treatment Approach

<table>
<thead>
<tr>
<th>Disease Extent</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_1N_{0-1}$ or $T_2N_0$</td>
<td>Surgery or RT</td>
</tr>
<tr>
<td>$T_2N_1$ or $T_{3-4}$ or $N_{2-3}$</td>
<td>Combined modality</td>
</tr>
<tr>
<td>Recurrent or $M_1$</td>
<td>Surgery and/or RT Combined modality Chemotherapy</td>
</tr>
</tbody>
</table>
Concurrent Chemoradiotherapy
## The Debate Over Therapeutic Sequence: MACH-NC Findings

<table>
<thead>
<tr>
<th>Design (No. of Studies/No. of Subjects)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Chemotherapy Effect (P-value)</th>
<th>Absolute Benefit 2 Years</th>
<th>Absolute Benefit 5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant¹ (8/1854)</td>
<td>0.98 (0.85-1.19)</td>
<td>0.74</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Neoadjuvant¹ (31/5269)</td>
<td>0.95 (0.88-1.01)</td>
<td>0.10</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Concurrent¹ (26/3727)</td>
<td>0.81 (0.76-0.88)</td>
<td>&lt; 0.0001</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Total¹ (65/10,850)</td>
<td>0.90 (0.85-0.94)</td>
<td>&lt; 0.0001</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of Trials</th>
<th>No. of Subjects</th>
<th>Difference at 5 Years</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF induction²</td>
<td>15</td>
<td>2487</td>
<td>5%</td>
</tr>
</tbody>
</table>

MACH-NC: Meta-Analysis of Chemotherapy in Head and Neck Cancer; PF=cisplatin + fluorouracil

Concurrent Therapy: Standard of Care

- Cisplatin 100 mg/m² days 1, 22, and 43 of RT

- RT standard fractionation, 70 Gy over 7 weeks (2-Gy fractions)

- Alternative Chemotherapy regimens:
  1- Weekly cisplatin 40mg/m²
  2- Weekly Cetuximab
  3- Weekly carboplatin auc 1.5-2+Paclitaxel 30-45mg/m²
RTOG 91-11 Induction Cisplatin/5-FU vs Concomitant Cisplatin vs RT Alone in Resectable SCC

Resectable stage III/IV SCC
- Glottic or supraglottic cancer
- Previously untreated

N = 515

- Primary end point: larynx preservation
- Secondary end point: LFS

LFS=laryngectomy-free survival

## RTOG 91-11
Larynx Preservation (LP) Trial

<table>
<thead>
<tr>
<th>Arm</th>
<th>Stomatitis*</th>
<th>LP rate (5yrs)</th>
<th>DFS (5yrs)</th>
<th>OS (5yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>24%</td>
<td>65.7%</td>
<td>27.3%</td>
<td>53.5%</td>
</tr>
<tr>
<td>Chemo → RT</td>
<td>24%</td>
<td>70.5%</td>
<td>38.6%</td>
<td>59.2%</td>
</tr>
<tr>
<td>ChemoRT</td>
<td>43%</td>
<td>83.6%</td>
<td>39.0%</td>
<td>54.6%</td>
</tr>
</tbody>
</table>

\* > or = Grade 3

Phase III Trial: Cetuximab + RT for SCC

Advanced SCC
• Stage III/IV
• N = 424

RT* + Cetuximab (400 mg/m^2, then 250 mg/m^2/wk)

RT* alone

*Choice of:
• Once-daily RT: 70 Gy in 35 fractions
• Twice-daily RT: 72.0-76.8 Gy in 60-64 fractions
• Concomitant boost: 72 Gy in 42 fractions

<table>
<thead>
<tr>
<th>Grade 3-5 Toxicity</th>
<th>RT Alone (N = 212)</th>
<th>RT + Cetuximab (N = 208)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis</td>
<td>52%</td>
<td>56%</td>
<td>.44</td>
</tr>
<tr>
<td>Acneiform Rash</td>
<td>1%</td>
<td>17%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Infusion Reaction</td>
<td>0%</td>
<td>3%</td>
<td>.01</td>
</tr>
<tr>
<td>Anemia</td>
<td>6%</td>
<td>1%</td>
<td>.006</td>
</tr>
</tbody>
</table>

Phase III: Cetuximab + RT for SCC: Results

Locoregional Control

47% vs 34% at 3 years
P < .01 at 3 years

OS

55% vs 45% at 3 years
P = .05 at 3 years

Sequential Chemoradiotherapy
TAX 324: Sequential Combined Modality Therapy
TPF vs PF Followed by Chemoradiotherapy

TPF: Docetaxel 75_{D1} + Cisplatin 100_{D1} + 5-FU 1000_{CI-D1-4} Q 3 weeks x3
PF: Cisplatin 100_{D1} + 5-FU 1000_{CI-D1-5} Q 3 weeks x 3

Carboplatinum - AUC 1.5 Weekly
Daily Radiotherapy
Surgery as Needed

TPF significantly improves survival and PFS compared with PF in an ICT regimen followed by CRT

# Taxane + PF Phase III Trials

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemo</strong></td>
<td>PF</td>
<td>DPF</td>
</tr>
<tr>
<td><strong>Subjects</strong></td>
<td>181</td>
<td>177</td>
</tr>
<tr>
<td><strong>Med PFS</strong></td>
<td>8.2 mo</td>
<td>11.0 mo</td>
</tr>
<tr>
<td><strong>Med OS</strong></td>
<td>14.5 mo</td>
<td>18.8 mo</td>
</tr>
<tr>
<td><strong>RR</strong></td>
<td>54%</td>
<td>68%</td>
</tr>
</tbody>
</table>

*P* < 0.05 for all outcomes except *P* = 0.06 for OS in Hitt study

Conclusions

• Overall survival advantage > 3 years with TPF sequential therapy
  – 40.5 month improvement in median overall survival at 3 years
  – 30% reduction in the risk of mortality ($P = 0.0058$)
    • Consistent with prior phase III trial (TAX 323)

• Patients received a median of 3 cycles of induction chemotherapy in the TPF and PF arms.

• In the TPF arm, 81% of patients went on to receive CRT.

• Grade 3/4 treatment-emergent adverse events:
  – Less stomatitis, thrombocytopenia, and lethargy in the TPF arm
  – More neutropenia and febrile neutropenia (any grade) in the TPF arm
Impact of Induction Chemotherapy (CT): Opposing Views and Ongoing Controversy

- **Pro:** Allows time to optimize patient medical status; Possible customization of RT dosing based on response to treatment; provides early treatment of distant micrometastatic disease

- **Con:** Induction CT may affect adversely compliance to subsequent concurrent CT/RT or choice of CT/RT regimen; adds 2-4 months to treatment
Clinical Scenarios to Consider Induction Therapy

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

- Indicated for gross residual disease
- Not indicated for pretreatment N1 disease that has achieved clinical complete response
- For pretreatment N2-3 disease, opinions vary:
  - When pretreatment neck disease is N2-3, some centers recommend routine ND regardless of response to chemoradiotherapy.
  - However, others will observe if a clinical complete response on PET scan 12 weeks post-therapy is achieved with chemoradiotherapy.

Adjuvant Chemoradiotherapy
EORTC 22931 and RTOG 9501 Phase III Trials: Adjuvant RT ± Concomitant Cisplatin

Resectable SCC
- Oral cavity, oropharynx, hypopharynx, larynx
- Stage III/IV (EORTC), high risk (RTOG)
- Previously untreated
  - N = 334 (EORTC)
  - N = 459 (RTOG)

Surgery

RT+ Cisplatin (100 mg/m², d1,22,43)
- EORTC: 66 Gy over 6.5 wks
- RTOG: 60-66 Gy over 6-6.6 wks

**Poor Risk Criteria**

**RTOG 9501**

- ≥ 2 nodes
- ECE
- +Margins

**EORTC 22931**

- Level IV/V (OC/OP)
- ECE
- +Margins
- Perineural disease
- Vascular emboli

ECE = extracapsular nodal extension; OC = oral cavity; OP = oropharynx

EORTC 22931 and RTOG 9501: Adjuvant RT ± Concomitant Cisplatin: Results

OS (EORTC)\(^1\)

![Graph showing OS (EORTC) results]

OS (RTOG)\(^2\)

![Graph showing OS (RTOG) results]

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RTOG 9501/EORTC 22931
Which prognostic risk factors are most important?

- Extracapsular nodal extension and + margins: significant benefit from chemoradiotherapy

- Trend toward benefit for stage III-IV disease, perineural invasion, vascular embolisms, and/or clinically enlarged level IV/V lymph nodes secondary to tumors in oral cavity or oropharynx

- No benefit in patients with 2 or more nodes but no extracapsular extension

Survivorship /Follow-Up

- Assess for recurrence/2nd primary/premalignant lesions
  - 1st year: Q 1-3 mos
  - 2nd year: Q 2-4 mos
  - 3rd – 5th year: Q 4-6 mos
  - > 5 years: Q 6-12 mos
- TSH q 6-12 months if neck irradiated
- Chest imaging as indicated
- Speech/Swallowing evaluation/rehabilitation as indicated
- Counsel regarding tobacco and alcohol use
- Integrate general medical care
- Once felt disease free, imaging of primary and neck not routinely indicated unless suspicious signs or symptoms
Palliative Chemotherapy
Management of Recurrent/Metastatic SCCHN

- Salvage surgery or re-irradiation
- Palliative systemic therapy
- Supportive care
- Chemotherapy +/- Targeted Therapy
- Immunotherapy
- Clinical Trials
EXTREME: Study Design

5-FU 1000 mg/m² d1-4 with
Cisplatin 100 mg/m² d1
or
Carboplatin AUC 5 d1

6 cycles maximum

5-FU 1000 mg/m² d1-4 with
Cisplatin 100 mg/m² d1
or
Carboplatin AUC 5 d1 plus
Cetuximab 250 mg/m²/week*
q 3 weeks

*Loading dose of 400 mg/m² on week 1

No treatment
POD or toxicity

Cetuximab
POD or toxicity

N = 442

EXTREME: First-Line Platinum/5-FU ± Cetuximab in Recurrent/Metastatic SCC: Survival

OS

Survival Probability

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

Survival Time (months)

Patients at Risk:
Platinum/5-FU 220
Cetuximab + Platinum/5-FU 222

173 127 83 65 47 19 8 1
184 153 118 82 57 30 15 3

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

Phase III randomized trial of chemotherapy with or without bevacizumab in patients with recurrent or metastatic squamous cell carcinoma of the head and neck: survival analysis of E1305, an ECOG-ACRIN Cancer Research Group trial

Athanassios Argiris, Shuli Li, Panayiotis Savvides, James Ohr, Jill Gilbert, Marshall A. Levine, Missak Haigentz Jr., Nabil F. Saba, Arnab Chakravarti, Chukwuemeka Ikpeazu, Charles Schneider, Harlan Pinto, Arlene A. Forastiere, Barbara Burtness

Argiris et al; Abstract 6000 ASCO 2017
**Phase III Randomized Trial of Platinum-based Chemotherapy With or Without Bevacizumab in Recurrent or Metastatic SCCHN (E1305)**

**STUDY SCHEMA**

**Recurrent or metastatic SCCHN**

**Performance status 0-1**

**No prior therapy for recurrent or metastatic SCCHN**

**Stratify by**
- Performance status
- Weight loss
- Prior radiotherapy
- Chemo regimen

**Option to discontinue chemotherapy after 6 cycles if maximum response**

**Arm A**
- Platinum doublet*
- Every 21 days until progression

**Arm B**
- Platinum doublet*
- + Bevacizumab 15 mg/kg
- Every 21 days until progression

*Choice of one of 4 chemotherapy regimens:*
1. cisplatin 100 mg/m² day 1, 5-FU continuous infusion 1000 mg/m²/day x 4 days
2. carboplatin AUC 6, day 1, 5-FU continuous infusion 1000 mg/m²/day x 4 days
3. cisplatin 75 mg/m² day 1, docetaxel 75 mg/m², day 1,
4. carboplatin AUC 6, day 1, docetaxel 75 mg/m², day 1,
   (in regimens 1 and 3, carbopatin substitution was allowed for specific severe cisplatin-related toxicities)

All patients received prophylactic ciprofloxacin on days 5-14

Option to discontinue chemotherapy after 6 cycles if maximum response.

Bevacizumab continued until progression.

Presented by: A. Argiris  Abstract 6000
### E1305 Patient Characteristics (I)

<table>
<thead>
<tr>
<th></th>
<th>Arm A: Chemo (N=200)</th>
<th>Arm B: Chemo +Bev (N=203)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>168 (84)</td>
<td>176 (87)</td>
</tr>
<tr>
<td>Female</td>
<td>32 (16)</td>
<td>27 (13)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>58 (32-86)</td>
<td>58 (29-82)</td>
</tr>
<tr>
<td><strong>Chemo doublet, N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin/Docetaxel</td>
<td>95 (48)</td>
<td>99 (49)</td>
</tr>
<tr>
<td>Cisplatin/5-FU</td>
<td>14 (7)</td>
<td>17 (8)</td>
</tr>
<tr>
<td>Carboplatin/Docetaxel</td>
<td>79 (40)</td>
<td>78 (38)</td>
</tr>
<tr>
<td>Carboplatin/5-FU</td>
<td>11 (6)</td>
<td>9 (4)</td>
</tr>
<tr>
<td><strong>ECOG Performance Status, N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>86 (43)</td>
<td>85 (42)</td>
</tr>
<tr>
<td>1</td>
<td>113 (57)</td>
<td>118 (58)</td>
</tr>
<tr>
<td><strong>Weight loss previous 6 months, N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5%</td>
<td>135 (68)</td>
<td>127 (63)</td>
</tr>
<tr>
<td>&gt;=5%</td>
<td>62 (31)</td>
<td>75 (37)</td>
</tr>
</tbody>
</table>
E1305 Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Median OS, months</th>
<th>P value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A: Chemo only</td>
<td>11.0</td>
<td>0.13</td>
<td>0.80 (0.67-1.05)</td>
</tr>
<tr>
<td>Arm B: Chemo + Bevacizumab</td>
<td>12.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
E1305 Progression-Free Survival

<table>
<thead>
<tr>
<th>Arm</th>
<th>Median PFS, months</th>
<th>P value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A: Chemo</td>
<td>4.4</td>
<td>0.0012</td>
<td>0.71 (0.58-0.87)</td>
</tr>
<tr>
<td>Arm B: Chemo + Bevacizumab</td>
<td>6.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Immunotherapy in Head and Neck Cancer
CheckMate 141 Study Design
Nivolumab VS. Chemotherapy

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.

Ferris et al.: NEJM 2016
### 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)
- **Nivolumab**: 36.0% (28.5–43.4)
- **Investigator’s Choice**: 16.6% (8.6–26.8)

#### No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Investigator’s Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>240</td>
<td>121</td>
</tr>
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</tr>
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<td>95% CI</td>
<td>(28.5–43.4)</td>
<td>(8.6–26.8)</td>
</tr>
</tbody>
</table>

#### Months

- 0  | 3  | 6  | 9  | 12 | 15 | 18
- 100| 90 | 80 | 70 | 60 | 50 | 40

#### Overall Survival (% of patients)

- 0  | 10 | 20 | 30 | 40 | 50 | 60
- 70 | 80 | 90 | 100| 0  | 0  | 0  |

- 1-year OS rate (95% CI)
  - **Nivolumab**: 36.0% (28.5–43.4)
  - **Investigator’s Choice**: 16.6% (8.6–26.8)
Phase 3 KEYNOTE-040 Study  
Pembrolizumab vs Chemotherapy

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

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

Pembrolizumab
200 mg IV Q3W for 2 y

R 1:1

Methotrexate 40 mg/m² QWe
OR
Docetaxel 75 mg/m² Q3W
OR
Cetuximab 250 mg/m² QWf

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

Limit of 2 prior therapies for R/M HNSCC. Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%.
Newly collected preferred. Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression.
Could be increased to 60 mg/m² QW in the absence of toxicity. Following a loading dose of 400 mg/m².
Overall Survival in ITT Population

**Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors.** Initially reported data: HR 0.82 (95% CI, 0.67-1.01), *P* = 0.0316. After the initial report, updated survival data were obtained for 4 patients.  

- **Pembrolizumab**  
  - Events, n: 179  
  - HR (95% CI): 0.81a (0.66-0.99)  
  - *P*: 0.0204b

- **SOC**  
  - Events, n: 201  

**Median (95% CI)**  
- **Pembrolizumab**: 8.4 mo (6.5-9.4)  
- **SOC**: 7.1 mo (5.9-8.1)

---

**N. at risk**  
- Time, months: 0  
  - 0: 247  
  - 1: 159  
  - 2: 103  
  - 3: 48  
  - 4: 14  
  - 5: 2  
  - 6: 0

- Time, months: 5  
  - 0: 248  
  - 1: 148  
  - 2: 82  
  - 3: 34  
  - 4: 10  
  - 5: 1  
  - 6: 0

---

aCox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors.  
bOne-sided *P* value based on the log-rank test stratified by the randomization stratification factors.  

Data cutoff date: May 15, 2017.
CHECKMATE-651: Phase III randomized, open-label study of nivolumab + ipilimumab compared to the EXTREME regimen as 1L treatment in patients with R/M SCCHN

Key Eligibility Criteria
- No prior systemic therapy for R/M disease except if chemotherapy was part of multimodal treatment ≤6 months prior to enrollment
- Tumor tissue required for HPV p16 (for OPC) and PD-L1 testing prior to randomization

Start Date: August 2016

Primary Endpoints: OS, PFS
Other Endpoints: ORR, time to deterioration, PD-L1 expression as biomarker
**KEYNOTE-048: Phase III, randomized, open-label, clinical trial of pembrolizumab in first line treatment versus active comparator in patients with R/M SCCHN without prior systemic chemotherapy**

**Key Eligibility Criteria**
- No prior systemic therapy in R/M setting, except if completed >6 months prior to locally advanced disease
- Available tumor biopsy for PD-L1 analysis
- Have results for HPV status for oropharyngeal cancer

**Primary Endpoint:** PFS
**Other Endpoints:** OS, PFS (by Immune-Related Response), ORR

**Start Date:** March 2015

**Randomized**
- **Pembrolizumab**
- **Pembrolizumab + Platinum + 5FU**
- **Active Comparator (cetuximab+ platinum+5-FU)**

Adapted from Mellman I et al 2011.
JAVELIN Head and Neck 100: Study Design

- A randomized double-blind phase III study of avelumab in combination with standard of care (SOC) chemoradiotherapy versus SOC chemoradiotherapy in the front-line treatment of SCCHN

Inclusion criteria:
- LA SCC oral cavity, oropharynx, larynx, hypopharynx
- HPV-; stage II, Iva, Ivb
- HPV+: T4 or N2c (AJCC 7) or N3
- ECOG PS = 0 or 1
- No prior therapy

Primary Endpoint: PFS by investigator per modified RECIST v1.1

Stratification Factors
- T stage (<T4 vs T4)
- N stage (N0/N1/2b vs N2c/N3)
- HPV (+ vs -) as measured by p16 IHC

Conclusions: Treatment of SCCHN in 2018

• Multiple options available
  – Concurrent chemoRT
  – Sequential therapy: TPF is the standard induction regimen
  – Robotic Surgery
  – Targeted therapy : Cetuximab/RT
  – PD-1 inhibitors : Clear activity shown in platinum resistant disease . Move to earlier lines of therapy in progress

• 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 and important research question