Head and Neck Cancer Update

Sandro V Porceddu
Director, Radiation Oncology Research
Princess Alexandra Hospital, Brisbane
Associate Professor, University of Queensland
President, Trans Tasman Radiation Oncology Group (TROG)
Overview of Head and Neck Talk

• Demographics and basic principles

• HPV-associated Oropharyngeal Cancer (OPC) vs non-HPV OPC/non-OPC disease

• Quality Care Delivery—the more we treat the better we get

• Emergence of immunotherapy in HNC
Overview of Head and Neck Talk

- Demographics and basic principles

- HPV-associated Oropharyngeal Cancer (OPC) vs non-HPV OPC/non-OPC disease

- Quality Care Delivery-the more we treat the better we get

- Emergence of immunotherapy in HNC
Head and Neck Cancer

- Developed world - 5% of all cancers
- Developing world - 5th common cancer
- Commonly mucosal squamous cell carcinoma
- Historically smoking & alcohol related
  - 5yr overall survival 40-60% for locally advanced disease
- Increasing incidence of HPV-associated oropharyngeal cancer (~80% of all oropharyngeal cancers)
  - 5yr overall survival 75-85%
Head and Neck Cancer in Australia in 2015

- New cases = 4,500
- M:F = 3:1
- 3.6% of all cancers
- Number of deaths = 1,000 (2% of all cancer deaths)
- Age-adjusted mortality rate is decreasing
- Chance of surviving at least 5 years is 68%

AIHW 2014
Head and Neck Cancer Treatment Modality

Surgery + PORT

Radiation therapy + systemic therapy

Surgery/PORT - non functioning larynx
Chemo-RT- functioning larynx
Curative chemo-radiotherapy for locally advanced head & neck cancer

- 7 weeks of XRT & concurrent cisplatin wks 1, 4, & 7
Overview of Head and Neck Talk

• Demographics and basic principles

• HPV-associated Oropharyngeal Cancer (OPC) vs non-HPV OPC/non-OPC disease

• Quality Care Delivery—the more we treat the better we get

• Emergence of immunotherapy in HNC
Increasing incidence of OPC
**HPV associated oropharyngeal cancer (OPC) vs non-HPV associated OPC/non OPC SCC**

<table>
<thead>
<tr>
<th>HPV-Related HNC</th>
<th>Environment-Related HNC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distinct entity</strong></td>
<td><strong>Traditional</strong></td>
</tr>
<tr>
<td>• Caused by high-risk HPV</td>
<td></td>
</tr>
<tr>
<td>– Sexual Practice</td>
<td></td>
</tr>
<tr>
<td>– viral oncogenes</td>
<td></td>
</tr>
<tr>
<td>• Male &gt; Female (3:1)</td>
<td></td>
</tr>
<tr>
<td>• Restricted to oropharynx</td>
<td></td>
</tr>
<tr>
<td>• “Good” prognosis</td>
<td></td>
</tr>
<tr>
<td>• Younger, fewer comorbidities</td>
<td></td>
</tr>
<tr>
<td>• Environmental mutagens</td>
<td></td>
</tr>
<tr>
<td>– Smoking</td>
<td></td>
</tr>
<tr>
<td>– alcohol</td>
<td></td>
</tr>
<tr>
<td>• Male &gt; Female (3:1)</td>
<td></td>
</tr>
<tr>
<td>• Throughout oral mucosa</td>
<td></td>
</tr>
<tr>
<td>• “Poor” prognosis</td>
<td></td>
</tr>
<tr>
<td>• Older, more comorbidities, 2nd cancers</td>
<td></td>
</tr>
</tbody>
</table>
Radiation Therapy Oncology Group 0129

Accrued 743 patients

No difference in OS or PFS

Arm 1:
Standard Fractionation
70 Gy/35 Fx/7 weeks
plus cisplatin 100 mg/m² on days 1, 22, 43

Arm 2:
Accelerated Fractionation by Concomitant Boost
72 Gy/42 Fx/6 weeks
plus cisplatin 100 mg/m² on days 1, 22

Gillison M. ASCO 2009, Orlando, abstract # 6003
Oropharyngeal Primary Site and p16 status

Survival outcomes by HPV status

- HPV Positive
- HPV Negative

5-year difference: 29%, 12-45

Overall Survival (%)

Patients at risk

<table>
<thead>
<tr>
<th></th>
<th>HPV Pos.</th>
<th>HPV Neg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>206</td>
<td>117</td>
</tr>
<tr>
<td>1</td>
<td>193</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>180</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>163</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>119</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>9</td>
</tr>
</tbody>
</table>

log-rank p<0.001

Gillison M. ASCO 2009, Orlando, abstract  # 6003
Risk Classification for Overall Survival by p-16, smoking & T-N Category (RTOG0129)

Oropharyngeal Carcinoma (N=260)

- p16-positive (N=187)
  - ≤10 pack-years (94)
    - N0-2a (29)
    - Low-risk (N=123 or 47%) 3-Y OS: 94%
  - >10 pack-years (93)
    - N2b-3 (64)
    - Intermediate-risk (N=73 or 28%) 3-Y OS: 67%

- p16-negative (N=73)
  - ≤10 pack-years (16)
    - T2-3 (9)
    - High-risk (N=64 or 25%) 3-Y OS: 42%
  - >10 pack-years (57)
    - T4 (7)

KK Ang et al NEJM 2010
DE-ESCALATION TRIALS
Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck

No increase in in-field toxicity

Bonner et al. NEJM 2006
A randomized trial of radiation with cetuximab or weekly cisplatin in low risk locoregionally advanced HPV-associated oropharyngeal cancer
Primary objective:

- To compare *symptom severity* between weekly cisplatin and RT versus weekly cetuximab and RT from baseline to week 20 (13 weeks post completion of radiotherapy)

Primary Endpoint:

- The primary endpoint is the area under the curve of *symptom severity* as measured by MDASI-HN Symptom Severity Score
Surgical de-escalation

RTOG 1221: Phase II Schema

**STRATIFY**

- T Stage
  1. T1
  2. T2
- N stage
  1. N1
  2. N2
- Zubrod Status
  1. 0
  2. 1

**RANDOMIZE**

Arm 1: eHNS* + Neck Dissection (Experimental Arm)
- "Risk-based" post-operative Adjuvant Therapy,
  +/- IMRT (60 Gy) +/- Weekly cisplatin **for high-risk patients with ≥ 5 metastatic nodes, extracapsular extension, or positive surgical margins on final surgical pathology**

Arm 2: Chemoradiotherapy (Control Arm)
- IMRT (70 Gy)
- Weekly cisplatin

**Eligible**

- Oropharyngeal SCC: Tonsil, BOT, GPC
- Stage III-IV: T1-2, N1-2b
- p16 NEGATIVE (IHC)

*eHNS = TLM or TORS
**Italicized text will be added at next protocol amendment (in progress)**
INTENSIFICATION TRIALS

Overcoming Hypoxia
Hypoxia determinant of outcome

Overgaard J. Radiother Oncol 2011
Overcoming Hypoxia

- Hypoxic cytotoxin eg Tirapazamine
- Hypoxic radiosensitizer eg Nimorazole
Tirapazamine, Cisplatin, and Radiation Versus Cisplatin and Radiation for Advanced Squamous Cell Carcinoma of the Head and Neck (TROG 02.02, HeadSTART): A Phase III Trial of the Trans-Tasman Radiation Oncology Group

Stage III or IV H&N SCC

**Randomise**

- **Arm 1** – Intergroup Protocol
  - Radiation + cisplatin
- **Arm 2** – TROG Protocol
  - Radiation + cisplatin + tirapazamine
Overall Survival TROG 02.02

- Estimated percentage surviving
- Years following randomisation

Comparison:
- CIS
- CIS/TPZ

Hazard ratio 95% CI

Rischin D et al, J Clinic Oncol 2010
Failure Free Survival

Estimated percentage surviving and failure-free

Years following randomisation

CIS
CIS/TPZ

Hazard ratio 95% CI
CIS/TPZ : CIS

2P = 0.96

Locoregional Failure

Estimated percentage locoregional failure-free

Years following randomisation

CIS
CIS/TPZ

Hazard ratio 95% CI
CIS/TPZ : CIS

2P = 0.44

Rischin D et al, J Clinic Oncol 2010
P16 negative patients only

Overall Survival (%)

- p16+ (n = 106)
- p16- (n = 79)

HR = 0.36; P = .004
2-year OS: 91% & 74%

Locoregional Failure Free (%)

- CIS/TPZ (n = 41)
- CIS (n = 38)

HR = 0.33; P = .13
2-year OS: 92% & 81%

No. at risk
p16+ 106 100 52 8 0
p16- 79 67 39 16 0
CIS/TPZ 41 33 22 8 0
CIS 38 29 16 7 0
• TROG Tirapazamine study did not stratify for HPV status

• Hypoxia is not a determinant of outcome in HPV-associated OPC

• Role of hypoxic cytotoxin unanswered in HPV-negative OPC and non-OPC HNC
A blind randomized multicenter study of accelerated fractionated chemo-radiotherapy with or without the hypoxic radiosensitizer nimorazole (Nimoral), using a 15 gene signature for hypoxia in the treatment of HPV/p16 negative squamous cell carcinoma of the head and neck.

EORTC 1219 ROG-HNCG
TROG 14.03
HPV/p16 negative
Stage III - IV (T1-4, N0-3)
Oropharynx
Larynx
Hypopharynx

RANDOMIZATION

Radiation therapy + cisplatin + placebo

Radiation therapy + cisplatin + nimorazole (oral tablet daily before RT)

Accrual Target 640 patients
1st primary objective:

- To evaluate in a randomized trial, whether the hypoxic cell radiosensitizer Nimorazole can improve the effect of primary curative accelerated fractionated concomitant chemo-radiotherapy with Cisplatin given to patients with locally advanced HPV/p16 negative HNSCC
2nd primary objective:

• To investigate if the patients who may have such benefit can be predicted by the use of a hypoxic gene profile, i.e. if the treatment benefit is larger and essentially restricted to the subset of patients who are hypoxic cell signature positive
Overview of Head and Neck Talk

• Demographics and basic principles

• HPV-associated Oropharyngeal Cancer (OPC) vs non-HPV OPC/non-OPC disease

• Quality Care Delivery—the more we treat the better we get

• Emergence of immunotherapy in HNC
Critical Impact of Radiotherapy Protocol Compliance and Quality in the Treatment of Advanced Head and Neck Cancer: Results From TROG 02.02

Lester J. Peters, Brian O’Sullivan, Jordi Giralt, Thomas J. Fitzgerald, Andy Trott, Jacques Bernier, Jean Bourhis, Kally Yuen, Richard Fisher, and Danny Rischin
Study was powered to detect a 20% difference in OS with Tirapazamine.
Time to locoregional failure

Estimated percentage locoregional failure-free

2-year LRF rates:
- 23% LRF - comp RT
- 24% LRF - no adv impact
- 47% LRF – adv impact

$2P < 0.0001$

Rischin D et al, J Clinic Oncol 2010
Table 3. Investigator Factors (country and enrollment bracket) Analyzed for Adverse Impact on Tumor Control Probability After Secondary Review (n = 818)

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of Patients</th>
<th>Number With Major Adverse Impact</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western Europe C</td>
<td>39</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Oceania A</td>
<td>164</td>
<td>8</td>
<td>5.2</td>
</tr>
<tr>
<td>North America A</td>
<td>101</td>
<td>6</td>
<td>5.9</td>
</tr>
<tr>
<td>Eastern Europe A</td>
<td>48</td>
<td>5</td>
<td>10.4</td>
</tr>
<tr>
<td>South America A</td>
<td>54</td>
<td>6</td>
<td>11.1</td>
</tr>
<tr>
<td>Western Europe B</td>
<td>67</td>
<td>8</td>
<td>11.9</td>
</tr>
<tr>
<td>Western Europe E</td>
<td>25</td>
<td>3</td>
<td>12.0</td>
</tr>
<tr>
<td>Oceania B</td>
<td>16</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>Western Europe A</td>
<td>127</td>
<td>17</td>
<td>13.4</td>
</tr>
<tr>
<td>South America B</td>
<td>42</td>
<td>6</td>
<td>14.3</td>
</tr>
<tr>
<td>Eastern Europe B</td>
<td>28</td>
<td>4</td>
<td>14.3</td>
</tr>
<tr>
<td>North America B</td>
<td>63</td>
<td>10</td>
<td>15.9</td>
</tr>
<tr>
<td>Western Europe D</td>
<td>30</td>
<td>5</td>
<td>16.7</td>
</tr>
<tr>
<td>Western Europe F</td>
<td>6</td>
<td>2</td>
<td>33.3</td>
</tr>
<tr>
<td>Western Europe G</td>
<td>4</td>
<td>2</td>
<td>50.0</td>
</tr>
<tr>
<td>Eastern Europe C</td>
<td>14</td>
<td>12</td>
<td>82.9</td>
</tr>
<tr>
<td>Enrollment bracket</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4 (26 centers)</td>
<td>57</td>
<td>17</td>
<td>29.8</td>
</tr>
<tr>
<td>5-9 (22 centers)</td>
<td>130</td>
<td>28</td>
<td>21.5</td>
</tr>
<tr>
<td>10-19 (22 centers)</td>
<td>279</td>
<td>33</td>
<td>11.8</td>
</tr>
<tr>
<td>≥ 20 (11 centers)</td>
<td>352</td>
<td>19</td>
<td>5.4</td>
</tr>
</tbody>
</table>

NOTE. P < .001 for country and enrollment bracket. Letters refer to countries in each region ranked in order of number of patients enrolled.
Institutional Clinical Trial Accrual Volume and Survival of Patients With Head and Neck Cancer

Evan J. Wuthrick, Qiang Zhang, Mitchell Machtay, David I. Rosenthal, Phuc Felix Nguyen-Tan, André Fortin, Craig L. Silverman, Adam Raben, Harold E. Kim, Eric M. Horwitz, Nancy E. Read, Jonathan Harris, Qian Wu, Quynh-Thu Le, and Maura L. Gillison
Institutional Clinical Trial Accrual Volume and Survival of Patients With Head and Neck Cancer

Evan J. Wuthrick, Qiang Zhang, Mitchell Machtay, David I. Rosenthal, Phuc Felix Nguyen-Tan, André Fortin, Craig L. Silverman, Adam Raben, Harold E. Kim, Eric M. Horwitz, Nancy E. Read, Jonathan Harris, Qian Wu, Quynh-Thu Le, and Maura L. Gillison

\[ P < .001 \]

\[ (P = .002) \]
In our analysis, measured deviations from protocol therapy did not entirely explain differences in OS and PFS by accrual volume. Only approximately 20% of the effect of accrual volume on OS and PFS could be explained by poor compliance with protocol-specified radiotherapy. “
Advances in Radiation Therapy

- Radiation Therapy is associated with significant acute toxicity & long term toxicity

- Highly conformal treatments with sparing of normal organs & tissues while delivering high doses to the tumour

Intensity Modulated Radiation Therapy
Overview of Head and Neck Talk

- Demographics and basic principles

- HPV-associated Oropharyngeal Cancer (OPC) vs non-HPV OPC/non-OPC disease

- Quality Care Delivery—the more we treat the better we get

- Emergence of immunotherapy in HNC
EMERGENCE OF IMMUNOTHERAPY
Cancer Immunotherapy

- New anti-cancer immunotherapies licensed
- Many more in development
- Long term remissions
Immune cells can kill cancer

T- cells

Tumour cells

tumour cell killing
Immune response to cancer

dendritic cells

tumour site

killing

Tc activation

lymph node
Immune response to cancer

dendritic cells

tumour site

killing

Tc activation

lymph node
Immune response to cancer

dendritic cells

killing

tumour site

CTLA-4

Tc activation

lymph node
the immune system has ‘brakes’

Activation

Downregulation

‘super’-activation

CTLA-4

anti-CTLA-4

anti-CTLA-4
taking the 'brakes off'

dendritic cells

tumour site

Anti- CTLA-4

Tc activation

lymph node
taking the ‘brakes off’

dendritic cells

Anti- CTLA-4

Tc activation

lymph node

tumour site
Anti-CTLA4

Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma

Giao Q. Phan¹, James C. Yang¹, Richard M. Sherry¹, Patrick Hwu¹, Suzanne L. Topalian¹, Douglas J. Schwartzentrube Nicholas P. Restifo¹, Leah R. Haworth¹, Claudia A. Seipp¹, Linda J. Freezer¹, Kathleen E. Morton¹, Sharon A. Mavroukakis¹, Paul H. Duray¹, Seth M. Steinberg¹, James P. Allison¹, Thomas A. Davis¹, and Steven A. Rosenberg¹

¹Surgery Branch, ¹Laboratory of Pathology, and ²Tumor Statistics and Data Management Section, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, ³Howard Hughes Medical Institute, Department of Molecular and Cell Biology, University of California, Berkeley, CA 94720; and Medarex, Inc., Princeton, NJ 08540

Contributed by James P. Allison, May 27, 2003

2011 ipilimumab licensed for treatment of advanced melanoma

Immune-related side effects

- pituitary
- skin
- liver
- colon
Immune response to cancer

- Dendritic cells
- CTLA-4
- PD-1
- Lymph node
- Tc activation

- Killing
Anti-PD1 Therapy

- Pembrolizumab-humanized monoclonal antibody that blocks interaction of PD-1 with its ligands PD-L1 & PD-L2, thereby promoting activity of tumour-specific effector T-cells
PD-1 blockade
Antitumor activity and safety of pembrolizumab in patients (pts) with advanced squamous cell carcinoma of the head and neck (SCCHN): Preliminary results from KEYNOTE-012 expansion cohort. Tanguy Y. Seiwert, The University of Chicago, Chicago, IL ★★★

Methods
Patients with advanced HNSCC irrespective of biomarker of HPV status. 200mg of pembrolizumab 3 weekly and evaluated every 8 weeks radiographically.

Results
99/132 were evaluable. Overall response rate 18.2% (95%CI; 11.1-27.2). >3AE 7.6% (any drug-related AE 47%); fatigue, appetite, pyrexia & rash. 58% had > 2 lines of therapy for recurrent disease. Biomarker evaluation ongoing.

Conclusion
Well tolerated with a meaningful ORR
Head and Neck Cancer Update

Keypoints

• HPV-associated OPC incidence is increasing and is a distinct clinical entity with a favourable prognosis compared with traditional HNC
• De-escalation trials in progress for HPV-associated OPC using targeted therapy and laser/TORS surgery
• Intensification trials ongoing for non-HPV associated OPC & advanced non-OPC HNC eg Nimorazole study
• HNC treatment outcomes reflect high quality RT and care in high volume centres
• Emergence of immunotherapy under investigation in HNC