Systemic Therapy in Advanced, Recurrent & Metastatic Setting HN Cancer

Dr Surender Beniwal
Dept of Medical Oncology
Overview

• Systemic treatment options for HNSCC
  – Cytotoxic chemotherapy for HNSCC
  – Current EGFR therapies
  – Emerging EGFR therapies
• Other emerging targets for HNSCC
• Metronomic therapy
HNSCC: Survival Rates by Stage of Disease

• High cures rates are achieved for localized and loco-regional disease using:
  – Surgery
  – Radiation
  – Chemoradiation
  – ± Induction chemotherapy

• Survival rates for recurrent/metastatic disease remain very poor

• Better treatment options are necessary

5-Yr Relative Survival Rate by Stage at Diagnosis[^6]

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>83%</td>
</tr>
<tr>
<td>Regional</td>
<td>59%</td>
</tr>
<tr>
<td>Distant</td>
<td>36%</td>
</tr>
</tbody>
</table>

Treatment Options for Recurrent/Metastatic HNSCC
Recurrent/Metastatic HNSCC: Cytotoxic Agents

- Active cytotoxic agents
  - Cisplatin, carboplatin, 5-FU, taxanes, methotrexate, ifosfamide, gemcitabine (for NPC), bleomycin, others
  - Methotrexate is FDA approved for use with HNSCC but no longer commonly used in the US

- First-line therapy
  - For patients with good PS: historically platinum-based doublet (eg, cisplatin/5-FU or carboplatin/paclitaxel)
    - ORR: 30% to 40%; median OS: 6-9 mos regardless of specific drugs
    - Cetuximab commonly added to current treatment regimens
  - For patients with poor PS: use single agent or cetuximab

- Second-line therapy: taxanes, methotrexate, cetuximab

Anti-EGFR Therapy: Cetuximab

- Cetuximab is a chimeric IgG1 anti-EGFR antibody
  - May also stimulate immune system via ADCC
- Approved for HNSCC as a single agent, with chemotherapy (EXTREME study), with radiation (Bonner study)
- Efficacy data
  - Despite high EGFR expression levels in HNSCC, single-agent response rate is “only” 13% with SD rate of 33%
  - There is currently NO predictive biomarker available.

EXTREME: Platinum/5-FU With or Without Cetuximab in Recurrent/Metastatic HNSCC

Randomized phase III trial

- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, DCR, TTF, DoR, QoL, safety

Recurrent/metastatic HNSCC; no previous chemotherapy except for locally advanced disease > 6 mos prior to study entry; no nasopharyngeal carcinoma (N = 442)

Cetuximab + Carboplatin or Cisplatin + 5-FU (n = 222)

Carboplatin or Cisplatin + 5-FU (n = 220)

Up to 6 cycles: cetuximab 400 mg/m², then 250 mg/m²/wk until PD or unacceptable toxicity; carboplatin AUC 5 or cisplatin 100 mg/m² on Day 1; 5-FU 1000 mg/m² on Days 1-4 every 3 wks.

Cetuximab ± First-line Platinum in Recurrent or Metastatic HNSCC: OS

HR : 0.80 (95% CI: 0.64-0.99; P = .04)

Chemotherapy only (n = 220) 20
Chemo + cetuximab (n = 222) 36

Survival Probability

Survival Time (Mos)

Pts at Risk, n
CTX only 220
CET + CTX 222

ORR, %
Chemo + cetuximab (n = 222) 36
Chemotherapy only (n = 220) 20

0 3 6 9 12 15 18 21 24

10.1 mos
7.4 mos

1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.1

Cetuximab ± First-line Platinum in Recurrent or Metastatic HNSCC: Safety

<table>
<thead>
<tr>
<th>Grade 3/4 AEs in ≥ 5% of Pts, n (%)</th>
<th>Cetuximab + Chemotherapy (n = 219)</th>
<th>Chemotherapy Alone (n = 215)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3/4</td>
<td>Grade 4</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Any event</td>
<td>179 (82)</td>
<td>67 (31)</td>
<td>164 (76)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>49 (22)</td>
<td>9 (4)</td>
<td>50 (23)</td>
</tr>
<tr>
<td>Anemia</td>
<td>29 (13)</td>
<td>2 (1)</td>
<td>41 (19)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>24 (11)</td>
<td>0</td>
<td>24 (11)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>19 (9)</td>
<td>4 (2)</td>
<td>19 (9)</td>
</tr>
<tr>
<td>Skin reactions</td>
<td>20 (9)</td>
<td>0</td>
<td>1 (&lt; 1)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>16 (7)</td>
<td>2 (1)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Cardiac events</td>
<td>16 (7)</td>
<td>11 (5)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12 (5)</td>
<td>0</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>11 (5)</td>
<td>1 (&lt; 1)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>11 (5)</td>
<td>2 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>11 (5)</td>
<td>8 (4)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>10 (5)</td>
<td>2 (1)</td>
<td>10 (5)</td>
</tr>
</tbody>
</table>

*Comparing Grade 3 and 4 combined.

SPECTRUM:
Cisplatin + 5-FU ± Panitumumab in Recurrent/Met HNSCC

- Open-label, randomized phase III trial

**Stratified by previous treatment, primary tumor site, ECOG PS**

- Patients with distant metastatic and/or locally recurrent HNSCC, ECOG PS ≤ 1 (N = 657)

**Max six 3-wk cycles**

- Panitumumab 9 mg/kg Day 1
- Cisplatin 100 mg/m² Day 1
- 5-FU 1000 mg/m² Days 1-4 (n = 327)

- Cisplatin 100 mg/m² Day 1
- 5-FU 1000 mg/m² Days 1-4 (n = 330)

- Optional panitumumab maintenance q3w

- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, DOR, TTR, safety

Cisplatin + 5-FU ± Panitumumab in Recurrent/Met HNSCC: OS

- Subgroup analysis in p16-negative patients significant: 11.7 vs 8.6 mos ($P = .01$)
  - Despite questions about p16 IHC cutoff values, hypothesized that EGFR inhibitors may be ineffective in HPV+ tumors
  - Supported by lack of EGFR overexpression/amplification in HPV+ tumors

Additional Anti-EGFR TKIs in HNSCC

- Previously small molecule anti-EGFR TKI have been less effective for HNSCC

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<tr>
<th></th>
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<tbody>
<tr>
<td>Gefitinib</td>
<td>500 mg</td>
<td>Gefitinib</td>
<td>Gefitinib</td>
<td>Erlotinib</td>
</tr>
<tr>
<td></td>
<td>250 mg</td>
<td>500 mg</td>
<td>150 mg</td>
<td></td>
</tr>
<tr>
<td>Median PFS or TTP, mos</td>
<td>3.4</td>
<td>1.8</td>
<td>2.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>8.1</td>
<td>5.5</td>
<td>4.3</td>
<td>6.0</td>
</tr>
<tr>
<td>1-yr OS, %</td>
<td>29.2</td>
<td>19</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>ORR, %</td>
<td>10.6</td>
<td>1.4</td>
<td>8</td>
<td>4.3</td>
</tr>
</tbody>
</table>

- Afatinib: an irreversible EGFR/erbB2/erbB4 blocker (pan-HER blockade)
  - Evaluated for HNSCC vs cetuximab

Afatinib: An ErbB Family Blocker

• Has demonstrated preclinical activity on ErbB1 (EGFR/HER1), ErbB2 (HER2), and ErbB4 (HER4).

• Has shown clinical activity in solid tumors (e.g., in lung and breast cancer).

In Vitro Molecular Potency (nM):

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<tr>
<td>ErbB1</td>
<td>0.5</td>
</tr>
<tr>
<td>ErbB2</td>
<td>14</td>
</tr>
<tr>
<td>ErbB4</td>
<td>1</td>
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</table>

Phase II Study: Afatinib vs Cetuximab in Recurrent/Metastatic HNSCC

Metastatic/recurrent HNSCC after failure of platinum-based regimen (N = 124; 62 per arm)

Stratum: number of previous chemotherapies for R/M disease (0 or 1)

Primary endpoint: tumor shrinkage of target lesions in S1

Stage 1

CT/MRI every 8 wks

Stage 2

Afatinib 50 mg/day PO

Cetuximab 400/250 mg/m²/wk IV

Afatinib

Cetuximab

Continue until PD or undue AEs

Continue until PD or undue AEs

Maximum Tumour Shrinkage in Target Lesions

<table>
<thead>
<tr>
<th></th>
<th>Afatinib (n = 50)</th>
<th>Cetuximab (n = 55)</th>
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</thead>
<tbody>
<tr>
<td>≥ 20%</td>
<td>n = 8</td>
<td>n = 12</td>
</tr>
<tr>
<td>0% - &lt; 20%</td>
<td>n = 16</td>
<td>n = 17</td>
</tr>
<tr>
<td>&gt; -30% - &lt; 0%</td>
<td>n = 10</td>
<td>n = 19</td>
</tr>
<tr>
<td>≤ -30%</td>
<td>n = 16</td>
<td>n = 7</td>
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</table>

Investigator Review

<table>
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<tr>
<th></th>
<th>Afatinib</th>
<th>Cetuximab</th>
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</thead>
<tbody>
<tr>
<td>Total randomized, n</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>ORR (CR, PR), n (%)</td>
<td>10 (16.1)</td>
<td>4 (6.5)</td>
</tr>
<tr>
<td>95% CI</td>
<td>8.0-27.7</td>
<td>1.8-15.7</td>
</tr>
<tr>
<td>P value</td>
<td>.09</td>
<td>--</td>
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Independent Central Review

<table>
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<tr>
<th></th>
<th>Afatinib</th>
<th>Cetuximab</th>
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</thead>
<tbody>
<tr>
<td>Total randomized, n</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>ORR (CR, PR), n (%)</td>
<td>5 (8.1)</td>
<td>6 (9.7)</td>
</tr>
<tr>
<td>95% CI</td>
<td>2.7-17.8</td>
<td>3.6-19.9</td>
</tr>
</tbody>
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Afatinib vs Cetuximab: Treatment Duration

- Data suggest that afatinib may overcome cetuximab resistance in a fraction of patients; potential lack of cross-resistance

Afatinib: Ongoing Phase III Studies

**LUX - Head & Neck 1**
- Randomized, open-label phase III trial; second-line treatment: patients have progressed on previous platinum-based chemotherapy for recurrent/metastatic HNSCC
- N = 474
- Randomized 2:1
- Afatinib 40 mg once daily
- MTX 40 mg/m² IV weekly
- Continuous treatment until PD (or AEs requiring withdrawal)
- Primary endpoint: PFS

**LUX - Head & Neck 2**
- Randomized, double-blind, placebo-controlled phase III trial; primary unresected, stage III-IVB HNSCC; disease free (with or without neck dissection) after completed previous CRT
- N = 669
- Randomized post-CRT 2:1
- Afatinib 40 mg once daily
- Placebo 40 mg once daily
- Treatment for 18 mos (or until recurrence or unacceptable AEs)
- Primary endpoint: DFS

Other EGFR-Targeted Agents in Development

- Dacomitinib: EGFR/erbB2/erB4 irreversible TKI
  - Activity in HNSCC in single phase II trial
- MEHD7945A: EGFR/HER3 antibody
  - Currently in phase II testing for HNSCC vs cetuximab
  - Phase I data: MEHD7945A may overcome cetuximab resistance; heregulin identified as candidate predictive biomarker
- Sym004: polyclonal anti-EGFR antibody mix
  - Activity in HNSCC, potentially effective after cetuximab failure
- ABT-414: EGFR antibody–drug conjugate
  - Phase II testing

Emerging Novel Targets for HNSCC
The Cancer Genome Atlas (TCGA): Candidate Therapeutic Targets

<table>
<thead>
<tr>
<th>Oncogenes</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>0%</td>
</tr>
<tr>
<td>EPHA2</td>
<td>4%</td>
<td>0%</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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TSG</th>
<th>HPV- (n = 244)</th>
<th>HPV+ (n = 35)</th>
</tr>
</thead>
<tbody>
<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>82%</td>
<td>3%</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>58%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Targetable Genetic Changes in HNSCC

Oncogene
Tumor Suppressor Gene
- HPV- incidence
- HPV+ incidence

MAPK pathway activation

mTOR

PI3K-AKT pathway activation

MAPK pathway activation

mTOR

PI3K-AKT pathway activation

SRC and STAT pathway activation

Drugs in Development for HNSCC

- **PI3K pathway**
  - BKM120 + cetuximab (phase II)
  - BYL719 + cetuximab (phase II)
  - Temsirolimus + cetuximab (phase II)
  - Rigosertib + cetuximab (phase II)
  - GDC-0980 (phase I HNSCC expansion cohort)

- **MET pathway**
  - Tivantinib + cetuximab (phase II)
  - Ficlatuzumab + cetuximab (phase II)

- **EGFR/HER3 pathway**
  - Afatinib + cetuximab ± paclitaxel (phase II)
  - LJM716 (phase I)

- **PD-1/PD-L1 immune checkpoints**
  - MK3475 (phase I/II)
  - Expansion cohort of other PD-1/ PD-L1 agents

- **FGFR pathway**
  - BGJ398 (phase II)

- **CDK4/6–cell cycle pathway**
  - Palbociclib (phase I)
  - LEE011 (phase I)
METRONOMIC CHEMOTHERAPY

• Frequent administration

• Low doses (1/10\textsuperscript{th}–1/3\textsuperscript{rd} of the maximum tolerated dose [MTD]) of drugs

• Shorter intervals without interruption.
METRONOMIC CHEMOTHERAPY

• MC exerts its anti-cancer activity-
  • Inhibiting tumor angiogenesis,
  • Stimulating anticancer immune response and
  • Stimulating tumor dormancy
  • Immunomodulatory effects
### Metronomic chemotherapy clinical trials in HNSCC patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Patients (n)</th>
<th>Protocol (n patients)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patil et al.</td>
<td>2015</td>
<td>phase II</td>
<td>110</td>
<td>celecoxib + methotrexate (57); cisplatinum (53)</td>
<td>OS 101 vs 66 days; PFS 249 vs 152 days</td>
</tr>
<tr>
<td>Pai et al.</td>
<td>2013</td>
<td>retrospective</td>
<td>64</td>
<td>celecoxib + methotrexate (32); no MC (32)</td>
<td>2-year DFS 94.6 % vs 75.4 %</td>
</tr>
<tr>
<td>Penel et al.</td>
<td>2010</td>
<td>randomised</td>
<td>88</td>
<td>cyclophosphamide (44); megestrol acetate (44)</td>
<td>2-month PFS 20.5 % vs 9 %; median OS 195 vs 144 days</td>
</tr>
</tbody>
</table>
Conclusions

• HNSCC is the 6th most common malignancy worldwide, and treatment options remain an unmet needs for patients with this disease.
• EGFR has been shown to be effect target for treatment; additional EGFR targeted agents in development.
• Evolving understanding of genetic profiling in patients with HNSCC may allow for development of additional targeted therapy.
  – **Promising new targets include**: PI3K, FGFR, CCND1, PD1/PD-L1
  – MC is a practical option
THANKS