Keynote Lecture 1 - Genomics and precision Medicine in H&N Cancer: Current Status and Future Perspectives

Tongyu Lin, MD, PhD
Cancer Center Sun Yat-Sen University
Guangzhou, China
Epidemiology

- Sixth most common cancer worldwide
  - 650,000 cases and 200,000 deaths/year

- Both incidence and mortality are higher in developing countries

Estimated New Cancer Cases and Deaths (Thousands) by Sex: China, 2015*

<table>
<thead>
<tr>
<th>SITE</th>
<th>ICD-10</th>
<th>INCIDENCE</th>
<th></th>
<th></th>
<th>MORTALITY</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lip, oral cavity, &amp; pharynx (except nasopharynx)</td>
<td>C00-C10, C12-C14</td>
<td>48.1</td>
<td>31.1</td>
<td>16.9</td>
<td>22.1</td>
<td>15.3</td>
<td>6.8</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>C11</td>
<td>60.6</td>
<td>43.3</td>
<td>17.3</td>
<td>34.1</td>
<td>24.9</td>
<td>9.2</td>
</tr>
<tr>
<td>Esophagus</td>
<td>C15</td>
<td>477.9</td>
<td>320.8</td>
<td>157.2</td>
<td>375.0</td>
<td>253.8</td>
<td>121.3</td>
</tr>
</tbody>
</table>

Incidence and Mortality of Top 10 Common Cancer in China
SCCHN, squamous cell carcinoma of the head and neck; NPC, nasopharyngeal cancer
Tonight, I’m launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes – 2015

**Precision medicine** is an emerging approach for disease prevention and treatment that takes into account people’s individual variations in genes, environment, and lifestyle.

The Precision Medicine Initiative will generate the scientific evidence needed to move the concept of precision medicine into clinical practice.

• ‘Moonshot initiative’-2016
Personalized Cancer care
Precision Medicine of Head and Neck Cancer

Tumor-based heterogeneity
- Site
- Stage
- Genetic alterations
- Predictive markers
- Prognostic markers

Patient-based heterogeneity
- Pharmacogenomics
- Co-morbidities (HBV, HIV)
- Experience with prior therapies
- Age
- PS
- Financial implications
Outline

Tumor-based Heterogeneity of SCCHN

- Stage
- Site
- Genetic alterations
- Predictive markers
- Prognostic markers
Why do we Need Individualized Treatment in SCCHN?

SCCHN is a heterogeneous disease that requires an individualized approach to treatment in order to achieve specific goals.
Current Treatment Options of Head and Neck Cancers

Early and locoregionally advanced SCCHN
- Surgery
- Radiotherapy
- Adding chemotherapy to radiotherapy

R/M HNSCC
- Platinum-based backbone
- Platinum, fluorouracil, and cetuximab-The only regimen to demonstrate survival superiority

multi-modality treatment
- Multidisciplinary team (MDT)
Advances in Head and Neck Cancer

**Development**

- Radiotherapy accuracy technology improved
- Transoral robotic surgery in OPC
- The development of immunotherapy for head and neck cancer

**Further study**

- BSC and long-term survival and QOL need further investigation
- Squamous cell carcinoma in the neck without a detectable primary site
- The biomarker exploration of EGFR inhibitors

### Are Appropriate Structures and Tools Available to Achieve Individualized Treatment?

<table>
<thead>
<tr>
<th>Section</th>
<th>Details</th>
</tr>
</thead>
</table>
| **Diagnostics** | • Clinical diagnosis and staging well established  
• Biomarker development ongoing |
| **MDTs** | • Becoming widespread in many countries  
• No specific culture supporting MDT team working |
| **Treatments** | • Multidisciplinary developments in surgery, RT, CT, targeted therapy and their combinations  
• Active research for new agents |
| **Strategies** | • Assessment of individuals for RT- vs surgery-based strategy  
• Optimization of new drug combination/sequence required  
• Individualized supportive care necessary |
| **Assessment tools** | • Many quality of life (QoL) tools available – optimal use in daily practice?  
• Biomarkers for efficacy and safety required |
Outline

Tumor-based Heterogeneity of SCCHN

- Stage
- Site
- Genetic alterations
- Predictive markers
- Prognostic markers
TCGA: Integrated Analysis of Genomic Alterations of HNSCC (n = 279)

Comprehensive Genomic Characterization of HNSCCs

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-associated tumors</td>
<td>• mutations of the oncogene PIK3CA</td>
</tr>
</tbody>
</table>
| novel alterations                            | • loss of TRAF3  
• amplification of the cell cycle gene E2F1                                                                                     |
| Smoking-related HNSCCs                       | • Near universal loss-of-function TP53 mutations  
• CDKN2A inactivation with frequent copy number alterations including amplification of 3q26/28 and 11q13/22 |
| subgroup of oral cavity tumours with favourable clinical outcomes | • Infrequent copy number alterations in conjunction with activating mutations of HRAS or PIK3CA  
• Inactivating mutations of CASP8,NOTCH1 and TP53                                                                                 |
| Other distinct subgroups                     | • loss-of-function alterations of the chromatin modifier NSD1  
• WNT pathway genes AJUBA and FAT1  
• activation of oxidative stress factor NFE2L2, mainly in laryngeal tumours                                                      |

## Commonly Mutated Genes in HNSCC Sequencing Studies

<table>
<thead>
<tr>
<th>Mutated gene</th>
<th>Gene class</th>
<th>% mutated genes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TP53</strong></td>
<td>TSG</td>
<td>47</td>
</tr>
<tr>
<td><strong>NOTCH1</strong></td>
<td>TSG</td>
<td>15</td>
</tr>
<tr>
<td><strong>CDKN2A</strong></td>
<td>TSG</td>
<td>9</td>
</tr>
<tr>
<td><strong>PIK3CA</strong></td>
<td>Oncogene</td>
<td>6</td>
</tr>
<tr>
<td><strong>FBXW7</strong></td>
<td>TSG</td>
<td>5</td>
</tr>
<tr>
<td><strong>HRAS</strong></td>
<td>Oncogene</td>
<td>4</td>
</tr>
<tr>
<td><strong>SYNE1</strong></td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>FAT1</strong></td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>MLL2</strong></td>
<td>TSG</td>
<td>NA</td>
</tr>
<tr>
<td><strong>CASP8</strong></td>
<td>TSG</td>
<td>NA</td>
</tr>
<tr>
<td><strong>PTEN</strong></td>
<td>TSG</td>
<td>NA</td>
</tr>
<tr>
<td><strong>NSD1</strong></td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>MLL3</strong></td>
<td>TSG</td>
<td>NA</td>
</tr>
<tr>
<td><strong>EP300</strong></td>
<td>TSG</td>
<td>NA</td>
</tr>
</tbody>
</table>

Pathway Analysis in SCCHN

**EGFR pathway**
- Over 90% SCCHN show EGFR overexpression\(^1\)

**HPV infection**
- 53% of oropharyngeal tumors positive for HPV16\(^2\)
- HPV+ tumors show higher CIN than HPV- tumors\(^2\)

**PI3 kinase pathway**
- Most frequently mutated oncogenic pathway in 151 SCCHN tumors \(^3\)
- Only stage IV tumors harbored multiple mutations \(^3\)

CIN, Chromosome instability

EGFR Overexpression in SCCHN is Linked to Tumor Pathogenesis and Poor Prognosis

- EGFR activation is involved in tumor growth\(^1\)
- EGFRs are overexpressed in many types of cancer, including most SCCHN\(^2\)
- EGFR expression is linked to reduced overall survival in SCCHN\(^3\)

EGFR is a rational therapeutic target in SCCHN

EGFR Overexpression in SCCHN is Linked to Tumor Pathogenesis and Poor Prognosis

- EGFR activation is involved in tumor growth\(^1\)
- EGFRs are overexpressed in many types of cancer, including most SCCHN\(^2\)
- EGFR expression is linked to reduced overall survival in SCCHN\(^3\)

<table>
<thead>
<tr>
<th>Type of tumor</th>
<th>Overexpressing EGFR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck</td>
<td>80–100</td>
</tr>
<tr>
<td>Breast</td>
<td>14–91</td>
</tr>
<tr>
<td>Renal</td>
<td>50–90</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>40–80</td>
</tr>
<tr>
<td>Colon</td>
<td>25–77</td>
</tr>
<tr>
<td>Ovary</td>
<td>35–70</td>
</tr>
<tr>
<td>Glioma</td>
<td>40–63</td>
</tr>
<tr>
<td>Pancreas</td>
<td>30–50</td>
</tr>
<tr>
<td>Bladder</td>
<td>31–48</td>
</tr>
</tbody>
</table>

EGFR is a rational therapeutic target in SCCHN

EGFR Overexpression in SCCHN is Linked to Tumor Pathogenesis and Poor Prognosis

- EGFR activation is involved in tumor growth\(^1\)
- EGFRs are overexpressed in many types of cancer, including most SCCHN\(^2\)
- EGFR expression is linked to reduced overall survival in SCCHN\(^3\)

EGFR is a rational therapeutic target in SCCHN

HPV+ and HPV– SCCHN Can Display Different Characteristics

Risk factors:
High-risk sexual practices, marijuana use (compared with smoking and alcohol, and poor oral hygiene for HPV–)\(^1,2\)

Incidences\(^4,5\)
Growing incidence vs HPV–tumors in Europe and US

Prognosis:
Lower mortality and risk of progression than HPV– (oropharyngeal SCCHN)\(^3\)

Patient profile\(^2\):
Younger age (by ~5 years) vs HPV–

HPV+ and HPV– SCCHN Can Display Different Characteristics

Risk factors:
High-risk sexual practices, marijuana use (compared with smoking and alcohol, and poor oral hygiene for HPV–)¹,²

Incidence⁴,⁵
Growing incidence vs HPV–tumors in Europe and US

Prognosis:
Lower mortality and risk of progression than HPV– (oropharyngeal SCCHN)³

Patient profile²:
Younger age (by ~5 years) vs HPV–

However, HPV status should not be a factor when choosing appropriate treatment⁶

PIK3CA: The Most Common “Targetable” Genomic Alteration in HNSCC

Analysis of whole-exome sequencing data from 151 tumors

- PI3K pathway: Be the most frequently mutated oncogenic pathway (30.5%)
- Only stage IV tumors harbored multiple mutations
- PIK3CA mutations were sensitive to an mTOR/PI3K inhibitor (BEZ-235)

Tumor-based Heterogeneity of SCCHN

Outline

- Stage
- Site
- Genetic alterations
- Predictive markers
- Prognostic markers
Anti-EGFR monoclonal antibodies (mAb)

EGFR tyrosine kinase inhibitors (TKI)

- Cetuximab
- Zalutumumab
- Panitumumab
- Nimotuzumab

- MEHD7945A
- Ertumaxomab
- Lymphocyte T
- CD3
- Catomaxomab

- Figitumumab
- Foretinib
- IGF-1R
- C-Met

- Erlotinib
- Gefitinib
- Lapatinib
- Afatinib
- Dacomitinib

- Vandetanib

- BKM 120, BYL 719
- Perifosine
- PI3K
- Akt
- mTOR

- Everolimus, Temsirolimus, Rapamycin

- Bortezomib
- Proteasome
- Degradation of IkB
- Activation of NFkB

- IPI-926
- mRNA

- HSP

- EGFR AS DNA

- Transcription

- HAT
- Ac
- Ac
- Ac
- HDAC

- Romidepsin, Vorinostat

- VEGFR
- PDGFR, c-kit, RET...

- Cediranib
- Sunitinib
- VEGF
- Bevacuzumab
Anti-EGFR monoclonal antibodies (mAb)

EGFR tyrosine kinase inhibitors (TKI)

Anti vascular endothelial growth factor (VEGF)
Anti-EGFR monoclonal antibodies (mAb)

EGFR tyrosine kinase inhibitors (TKI)

Blockage of multiple HER receptors

The signal transducer and activation of transcription (STAT) pathway

Blocking the PI3K/Akt/mTOR pathway

Anti vascular endothelial growth factor (VEGF)
Anti-EGFR monoclonal antibodies (mAb)

EGFR tyrosine kinase inhibitors (TKI)

Blockage of multiple HER receptors

VEGF kinase inhibitors and multi-kinase inhibitors

The signal transducer and activation of transcription (STAT) pathway

Blocking the PI3K/Akt/mTOR pathway

Anti vascular endothelial growth factor (VEGF)
Anti-EGFR monoclonal antibodies (mAb)

EGFR tyrosine kinase inhibitors (TKI)

Blockage of multiple HER receptors

inhibitor of c-MET

IGF-1R inhibitors
- Figitumumab
- Foretinib

Blocking the PI3K/Akt/mTOR pathway
- BKM 120, BYL 719
- Perifosine
- Everolimus, Temsirolimus, Rapamycin

The signal transducer and activation of transcription (STAT) pathway

VEGF kinase inhibitors and multi-kinase Inhibitors
- Cediranib
- Sunitinib
- Vandetanib
- Bevazuzumab

Anti vascular endothelial growth factor (VEGF)
Right Treatment for Right Patient: Are Biomarkers the Answer?

Number of candidate biomarkers in SCCHN\textsuperscript{1-3}

Phase III Trials of Cetuximab With Radiotherapy or Platinum-Based Chemotherapy Improves Survival

**Locally Advanced HNSCC**
HR: 0.73 (0.56, 0.95), $P = 0.02$

**Recurrent/Metastatic HNSCC**
HR: 0.80 (0.64, 0.99), $P = 0.04$

Overall Survival

- RT + Cetuximab (≤8 doses)
- RT Alone
- Chemotherapy ≤6 cycles + Cetuximab (Med: 29 doses)
- Chemo Alone

**Overall Survival**

Δ 2.7 Months

Δ 20 Months

10%
## Non-Cetuximab Containing Randomized Trials in Recurrent/Metastatic SCCHN Anti-EGFR therapies

<table>
<thead>
<tr>
<th>Study/Reference</th>
<th>N</th>
<th>Regimen</th>
<th>RR (%)</th>
<th>PFS (mo)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPECTRUM/</td>
<td>65</td>
<td>PF(^2) + panitumumab</td>
<td>36(^*)</td>
<td>5.8(^{**})</td>
<td>11.1</td>
</tr>
<tr>
<td>Vermorken et al</td>
<td>7</td>
<td>PF(^2)</td>
<td>25(^*)</td>
<td>4.6(^{**})</td>
<td>9.0</td>
</tr>
<tr>
<td>2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZALUTE</td>
<td>28</td>
<td>Z + BSC (-MTX)</td>
<td>6</td>
<td>2.3(^{†})</td>
<td>6.7(^°)</td>
</tr>
<tr>
<td>Machiels et al,</td>
<td>6</td>
<td>BSC (optional MTX)(^a)</td>
<td>1</td>
<td>1.9(^{†})</td>
<td>6.7(^°)</td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| \(^a\)87% received MTX; \(^b\) Time to progression *P=0.007; **P=0.004; †P=0.001; ° P=0.0648

Detecting other alterations in the EGFR pathway that contribute to resistance may help select patients most likely to respond to treatment.
Response rate for ERBITUX+ cisplatin patients % (n=57)

No skin reaction: 7
Skin reaction: 33
Impact on EGFR Signaling

Clinical responder: Frozen biopsies of metastatic lesion, Agilent array

Pre-therapy: EGFR expressed

Post-therapy: One week cetuximab + carboplatin

EGFR inactivated by therapy

Courtesy of: Charles M. Perou, PhD.
Heterogeneous Impact on EGFR Signaling

- 16 tumors with serial biopsies from target lesion

Targeted therapies require great understanding of all the players in a pathway.
Access to tumor tissue is critical!
- 8 no significant change (all PD)
Outline

Tumor-based Heterogeneity of SCCHN

- Stage
- Site
- Genetic alterations
- Predictive markers
- Prognostic markers
Pathologic Features:
High frequency of basaloid tumors; Low p53 mutation rate; Expression of p16

HPV variants (e.g. HPV16, HPV18): Malignant transformation

- **HPV16**: Predominant variant of HPV;
  - Identified by its surrogate marker, p162;
  - Downregulated in SCCHN;
  - Upregulated in HPV+ cancers.

- **HPV detection**: HPV E6 oncogene expression;
  - HPV DNA.

HPV E6 and E7 oncoproteins disrupt tumor suppressor genes p53 and pRb, which control the cell cycle, leading to malignant transformation\textsuperscript{1–3}

- Functional inactivation of pRb by E7 leads to upregulation of p16\textsuperscript{4}

Potential Prognostic Indicators of Local Recurrence: HPV16 and p16 Positivity

- Retrospective study of 90 patients with oropharyngeal SCCHN

HPV16 DNA status significantly reduces incidence of tumor relapse ($P=.0371$)

HPV Status is a Strong and Independent Predictor of OS: RTOG 0129 and 0522

- Retrospective study of 181 patients with oropharyngeal SCCHN

Overall survival after disease progression for patients with p16-positive and p16-negative oropharyngeal carcinoma (OPC)

- 2-year OS after progression:
  - HPV16+: 54.6%
  - HPV 16-: 27.6%

Prognostic Significance of HPV in R/M HNSCC: An Analysis of ECOG1395 and 3301

- Retrospective study of 64 patients with 2 RCT first-line R/M oropharyngeal SCCHN

### SPECTRUM: Cisplatin + Fluorouracil ± Panitumumab

<table>
<thead>
<tr>
<th></th>
<th>p16-positive patients</th>
<th>p16-negative patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Panitumumab group</td>
<td>Control group</td>
</tr>
<tr>
<td>Died</td>
<td>42/57 (74%)</td>
<td>30/42 (71%)</td>
</tr>
<tr>
<td>Overall survival (months)</td>
<td>11.0 (7.3-12.9)</td>
<td>12.6 (7.7-17.4)</td>
</tr>
<tr>
<td>Progressed</td>
<td>54/57 (95%)</td>
<td>36/42 (86%)</td>
</tr>
<tr>
<td>Progression-free survival (months)</td>
<td>5.6 (4.4-6.5)</td>
<td>5.5 (3.4-6.7)</td>
</tr>
</tbody>
</table>

Data are n/N (%), median (95% CI), or hazard ratio (95% CI), unless otherwise stated.

*Table 6: Overall and progression-free survival in the two treatment groups by p16 status*
High Expression of PDL-1 in HPV+ HNSCC

PD-L1 Expression in HNSCC

Positive ×100

Positive ×400

Strong positive ×100

Strong positive ×400
### KEYNOTE-055
Phase 2 Trial in R/M HNSCC

- R/M HNSCC
- Resistant to platinum and cetuximab
- Measurable disease
- ECOG PS 0-1

![Pembrolizumab 200 mg Q3W](image)

### KEYNOTE-012
Phase 1b: HNSCC Cohorts

- R/M HNSCC
- PDL1+ (initial cohort)
- PDL1+ or PDL1- (expansion cohort)
- Measurable disease
- ECOG PS 0-1

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

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

---

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>Keynote 055</th>
<th>Keynote 012</th>
<th>PDL1 Positive (n = 88)</th>
<th>PDL1 Negative (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients With ≥6 Month Follow up N = 92</td>
<td>Total N = 192</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
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</tr>
<tr>
<td>ORR*</td>
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<td>SD</td>
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<tr>
<td>PD</td>
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<td></td>
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<tr>
<td>NA†</td>
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</tbody>
</table>

Overall Response

- PDL1 Positive: 17%
- PDL1 Negative: 12%

Hazard Ratio

- PDL1 Positive: 0.55
- PDL1 Negative: 0.89

HPV Positive (n = 92)

- Hazard Ratio: 0.56

HPV Negative (n = 86)

- Hazard Ratio: 0.73
Phase III Trial of Nivolumab vs Investigator Choice Chemotherapy in R/R HNSCC

<table>
<thead>
<tr>
<th></th>
<th>PDL1 Positive (n = 88)</th>
<th>PDL1 Negative (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response</td>
<td>17%</td>
<td>12%</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.55</td>
<td>0.89</td>
</tr>
<tr>
<td>HPV Positive (n = 92)</td>
<td>HPV Negative (n = 86)</td>
<td></td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.56</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Median OS, mo (95% CI) | HR (97.73% CI) | P value |
---|---|---|
Nivolumab (n = 240) | 7.5 (5.5, 9.1) | 0.70 (0.51, 0.96) | 0.0101 |
Investigator’s choice (n = 121) | 5.1 (4.0, 6.0) | |

1-year OS rate (95% CI) | 36.0% (28.5, 43.4) |
1-year OS rate (95% CI) | 16.6% (8.6, 26.8) |

Cetuximab, docetaxel or MTX
Future Perspectives
Liquid Biopsy in Precision Medicine
Early Detection - Saliva

Tumor DNA in saliva or plasma

Sensitivity

<table>
<thead>
<tr>
<th>Tumor location</th>
<th>Saliva</th>
<th>Plasma</th>
<th>Saliva or plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>100%</td>
<td>80%</td>
<td>100%</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>47%</td>
<td>91%</td>
<td>91%</td>
</tr>
<tr>
<td>Larynx</td>
<td>70%</td>
<td>86%</td>
<td>100%</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>67%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Yuxuan Wang et al., Sci Transl Med 2015;7:293ra104
## Potential of Liquid Biopsy in Precision Medicine: Landscape

### Metastatic

<table>
<thead>
<tr>
<th>Application</th>
<th>Diagnostic Indication</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard of care</td>
<td>Genotyping</td>
<td>Therapy selection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prognosis</td>
</tr>
<tr>
<td>Tumor burden</td>
<td>Early therapeutic response or resistance</td>
<td>Molecular Remission</td>
</tr>
<tr>
<td>Resistant disease</td>
<td>Tracking Resistance</td>
<td>Therapy selection</td>
</tr>
</tbody>
</table>

Presented By Luis Diaz at 2016 ASCO Annual Meeting
Potential of Liquid Biopsy in Precision Medicine: Landscape

### Resectable

<table>
<thead>
<tr>
<th>Application</th>
<th>Diagnostic Indication</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection</td>
<td>Minimal residual disease</td>
<td>Intensify chemotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Withhold chemotherapy</td>
</tr>
<tr>
<td>Recurrence tracking</td>
<td>Molecular relapse</td>
<td>Early intervention</td>
</tr>
</tbody>
</table>
### Potential of Liquid Biopsy in Precision Medicine: Landscape

#### Pre-malignant

<table>
<thead>
<tr>
<th>Application</th>
<th>Diagnostic Indication</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>molecular diagnosis</td>
<td>SOC treatment</td>
</tr>
<tr>
<td>Screening</td>
<td>occult disease detection</td>
<td>identify cancer high-risk population</td>
</tr>
</tbody>
</table>
Potential of Liquid Biopsy in Precision Medicine: Landscape

Future for ctDNA

**Incremental improvements in technology**
- Increase in comprehensive panels
- Limited by biology more that technology
- Need a biologic based discovery to drive dramatic improvement

**Clinical Application**
- Tumor genotyping in plasma will be integrate into routine practice – based on concordance studies
- High impact applications that drive improvements in OS will require prospective clinical trials and partnership with FDA.
Immunotherapy in SCCHN: Future Direction Cancer-Immunity Cycle

# Immunotherapy in SCCHN: Future Direction Combined with Chemotherapy

<table>
<thead>
<tr>
<th>Name</th>
<th>Phase (n)</th>
<th>Disease</th>
<th>Treatment</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keynote 048</td>
<td>III (780)</td>
<td>R/M HNSCC (first line)</td>
<td>Pembrolizumab + platin/5FU vs cetuximab/platin /5FU</td>
<td>PFS</td>
</tr>
<tr>
<td>KESTREL</td>
<td>III (628)</td>
<td>R/M HNSCC (first line)</td>
<td>Durvalumab +/- tremelimumab vs SOC</td>
<td>PFS, OS</td>
</tr>
<tr>
<td>CheckMate 651</td>
<td>III (490)</td>
<td>R/M HNSCC (first line)</td>
<td>Nivolumab + ipilimumab vs cetuximab/platin /5FU</td>
<td>OS, PFS</td>
</tr>
</tbody>
</table>

Immunotherapy in SCCHN: Future Direction
Combination with Other Immunotherapies

Combination CPI
- Durvalumab + tremelimumab
- Nivolumab + ipilimumab

Other combinations
- Nivolumab + epacadostat
- Pembrolizumab + epacadostat
- Urelumab + cetuximab
- Urelumab + nivolumab

Immunotherapy in SCCHN: Future Direction Combination With RT RADVAX™

Immunotherapy in SCCHN: Future Direction
HPV Associated HNSCC

• HPV specific therapeutic vaccins alone or in combination
  - ADXS11-001
  - INO 3112

• Adoptive T cell therapy

**Anti-PDL1**

Targeting PD-L1 blocks binding to PD-1 and B7.1, resulting in restoration of anti-cancer T cell activity\(^1\text{-}^3\).

PD-L2/PD-1 interaction is left intact, potentially preserving peripheral immune homeostasis\(^1\text{-}^4,^7\).

**Anti-PD1**

Targeting PD-1 blocks binding to PD-L1, leaving the interaction between PD-L1 and B7.1 intact\(^1,^8,^9\).

PD-L2/PD-1 interactions are inhibited, potentially affecting peripheral immune homeostasis\(^1,^4\text{-}^7\).
Drugs Approved to Target Genomic Pathways in Tumors
Drugs Approved to Target Genomic Pathways in Tumors

gefitinib, cetuximab
EGF
trastuzumab
HER2

growth factors (e.g., TGFβ)

hormones (e.g., Bombesin)

(e.g., Estrogen)

Glucose, AMP

survival factors (e.g., IGF1)

EGFR
Grb2
SOS
Ras
Raf
MEK
MAPK
MAPK
ERK

PKA
PKC
STK11
AMK
mTOR

nM2

NHR (e.g., ER)

Cell Proliferation (Cell Cycle)

Changes in Gene Expression

Cell Death (Apoptosis)

DNA damage sensor

Arf

MDM2

p53

Bax

Caspase 8

Bax

Bid

Caspase 9

Cytochrome C

Bcl 2

Bcl 2

FADD

Death factors (e.g., FasL)

Abnormality sensor

BAD

Mitochondria

BAD

Bim, etc

BAD

BAD

BAD

TGFβR

Smad

E2Fs

Cyclin D:CDK4

Rb

HPV E7

Cyclin E:CDK2

p27

p21

p15

p16

DNA damage sensor

ARF

MDM2

p53

Bax

Caspase 8

Bcl 2

FADD

Death factors (e.g., FasL)

Abnormality sensor

BAD

Mitochondria

BAD

Bim, etc

BAD

BAD

BAD

TGFβR

Smad

E2Fs

Cyclin D:CDK4

Rb

HPV E7

Cyclin E:CDK2

p27

p21

p15

p16

DKDAC

HDCAC

Vismodegib

Shh (Embryonic development)

siRNA (Embryonic development)

Smo

Ptc

Gli

Vorinostat, panobinostat, romidepsin, belinostat

HDCAC

palbociclib

temsirolimus

tofacitinib

ruxolitinib

CRIZOTINIB

ALK fusions

Cytochines (e.g., IL-3/6)

Cytokines

siltuximab, tocilizumab

CTLA-4

ipilimumab
2016 FDA Approved Drugs

- **Keytruda (pembrolizumab)**; Merck; For the treatment of **head and neck squamous cell cancer**, Approved August 2016
- **Opdivo (nivolumab)**; Bristol-Myers Squibb; For the treatment of recurrent or metastatic **squamous cell carcinoma of the head and neck**, Approved November 2016
Immunotherapy shows clinically meaningful responses in advanced HNSCC. Combination therapies will be required to boost response rates. Patient selection and biomarkers will be crucial for further development.

HPV-positive and HPV-negative HNSCC differs significantly.

Current treatment options as EGFR inhibitors are lacking a predictive biomarker in SCCHN. Studies are underway to explore biomarkers, which can predict targeted therapy.

SCCHN is a heterogeneous disease that requires an individualized approach to treatment.

Conclusion

1. SCCHN is a heterogeneous disease that requires an individualized approach to treatment.
2. Current treatment options as EGFR inhibitors are lack of predictive biomarker in SCCHN. Studies are underway to explore biomarkers, which can predict targeted therapy.
3. HPV-positive and HPV-negative HNSCC differs significantly.
4. Immunotherapy shows clinically meaningful responses in advanced HNSCC. Combination therapies will be required to boost response rates. Patient selection and biomarkers will be crucial for further development.
5. Liquid biopsy play a role in early detection of SCCHN. Further studies and improvement in technology are warranted.
Acknowledgement

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Patients and their families
Thanks for your attention
Expert Practice™
in Head and Neck Cancer