Immune checkpoint molecules

- Activating receptors: OX40, 4-1BB(CD137), ICOS etc.
- Inhibitory receptors: CTLA-4, PD-1, TIM-3, LAG-3 etc.

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- Overview of cancer immunity
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Current Status of Immune Check Point Inhibitors for Head and Neck Cancer

Department of medical oncology and hematology,
Kobe University Hospital, Japan
Naomi Kiyota

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Cycle of cancer immunity

- Priming and activation
- Trafficking of T cells
- Infiltration of T cells
- Recognition of tumor
- Killing of cancer cells
- Release of cancer cell Ag

Immune checkpoint molecules

- Activating receptors: OX40, 4-1BB(CD137), ICOS etc.
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- PD-1: binding PD-L1 on tumor cells to inhibit T-cell activation

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Tumor mutation burden

Malignant melanoma
- Treatment: anti-CTLA-4 Ab, Ipilimumab or Tremelimumab
- Mutation burden correlated with efficacy of anti-CTLA-4 Ab

Rizvi et al. SCIENCE, 2015

Snyder et al. NEJM, 2015

Inhibitory immune checkpoint receptors

- CTLA-4: central inhibitory receptor for T-cell activation
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Snyder et al. NEJM, 2015


Tumor mutation burden

Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma

Snyder et al. NEJM, 2015

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Tumor mutation burden

Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer

Snyder et al. NEJM, 2015
Tumor mutation burden

- Non-small cell lung cancer (NSCLC)
- Treatment: anti-PD-1 Ab, Pembrolizumab
- Mutation burden correlated with efficacy of anti-PD-1 Ab

HPV and PD-L1 expression

- More intense PD-L1 expression in HPV +ve HNC

HNC is an immunosuppressive disease

- Lower absolute lymphocyte counts
- Impaired NK-cell activity
- Poor antigen-presenting function
- Impaired TILs
- Increased activity of Treg
- Development of T cell tolerance to persistent viral infection

HPV positive OPC and PD-L1

- Increase in IFN-γ and CD8 mRNA in PD-L1+ cancers
- May reflect the down-regulation of anti-tumor immunity

Lyford Pike et al. Cancer Res. 73(6); 1733–41.

Strome et al. Cancer Res; 76(5); 1031–43, 2015

Ukpo et al. OP 181 46% 49% 34%

Kim et al. OP 133 68% 71% 61%

Lyford-pike et al. OP 27 59% 70% 29%

Badoual et al. OC, OP, HP 64 52% 63% 40%

Concha-Benavenete et al. N/A 134 60% 70% 43%

Zhang et al. NP 139 95% --

Hsu et al. NP 25 100% --


Tumor mutation burden

- Correlate with sensitivity of immune check point inhibition
- High mutation burden: Melanoma, NSCLC, CRC, HNC

HNC and PD-L1 expression

- Higher expression of PD-L1 in virus related HNC

<table>
<thead>
<tr>
<th>Author</th>
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<th>T</th>
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<tr>
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DCB: durable clinical benefit (PR or SD>6months)
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Tumor mutation burden

- Correlate with sensitivity of immune check point inhibition
- High mutation burden: Melanoma, NSCLC, CRC, HNC
Nasopharyngeal cancer and PD-L1

- PD-L1 expression: 95% of NPC
- Higher level of PD-L1 expression correlated with worse prognosis

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PD-1/PD-L1 inhibitors on development

<table>
<thead>
<tr>
<th>Target</th>
<th>Agents</th>
<th>company</th>
<th>Isotype and characteristics</th>
<th>phase</th>
<th>HNC</th>
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<td>Nivolumab</td>
<td>MedImmune/AZ</td>
<td>humanized IgG4</td>
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<td>Pembrolizumab</td>
<td>MSD</td>
<td>humanized IgG4</td>
<td>I-III</td>
<td>on going</td>
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<td>PDR-001</td>
<td>Novartis</td>
<td>humanized IgG4</td>
<td>II</td>
<td>on going</td>
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<td>PD-L1</td>
<td>MEDI4736 (Durvalumab)</td>
<td>MedImmune/AZ</td>
<td>Fc-modified humanized IgG1</td>
<td>I-III</td>
<td>on going</td>
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<tr>
<td></td>
<td>MPDL3280A (Avelumab)</td>
<td>Genentech/Roche</td>
<td>Fc-modified humanized IgG1</td>
<td>II</td>
<td></td>
</tr>
</tbody>
</table>

Clinical trials.gov

Cancer Cell 27, April 13, 2015
Randomized, global, phase 3 trial of the efficacy and safety of nivolumab versus investigator’s choice in patients with R/M SCCHN:

- Prior cetuximab treatment
- No active CNS metastases
- Documentation of p16 to determine
- Progression on or within 6 months of
- R/M SCCHN of the oral cavity, pharynx, or larynx
- HPV status

### HPV status

<table>
<thead>
<tr>
<th>HPV Status</th>
<th>Nivolumab (n = 240)</th>
<th>Investigator’s Choice (IC) (n = 236)</th>
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</thead>
<tbody>
<tr>
<td>HPV+</td>
<td>120 (50.0%)</td>
<td>116 (49.5%)</td>
</tr>
<tr>
<td>HPV-</td>
<td>120 (50.0%)</td>
<td>120 (50.5%)</td>
</tr>
</tbody>
</table>

### Summary of Anti-PD-1/PD-L1 for R/M HNSCC

- **CheckMate 141**
  - Key Criteria:
    - PD-L1-
    - HPV-/p16-
  - Key Outcomes:
    - ORR
    - mOS
    - DOR
  - Treatment:
    - Nivolumab
      - 3 mg/kg IV q2w
    - Investigator’s Choice
  - Key Statistics:
    - ORR: 30.2% vs. 10.0%
    - mOS: NR vs. 12.6 months
    - DOR: 5.2 months vs. 2.1 months

- **KEYNOTE-012**
  - Key Criteria:
    - PD-L1+
    - HPV+/p16+
  - Key Outcomes:
    - ORR
    - mOS
    - DOR
  - Treatment:
    - Nivolumab
      - 10 mg/kg Q2W
    - Investigator’s Choice
  - Key Statistics:
    - ORR: 40.4% vs. 29.9%
    - mOS: NR vs. 12.6 months
    - DOR: 2.1 months vs. 2.1 months

- **KEYNOTE-055**
  - Key Criteria:
    - PD-L1-
    - HPV-/p16-
  - Key Outcomes:
    - ORR
    - mOS
    - DOR
  - Treatment:
    - Nivolumab
      - 200 mg Q3W
    - Investigator’s Choice
  - Key Statistics:
    - ORR: 16.6% vs. 8.6%
    - mOS: NR vs. 28.5–43.4 months
    - DOR: 2.1 months vs. 2.1 months

- **CheckMate 141 vs. KEYNOTE-055**
  - Key Comparison:
    - ORR: 20.8% vs. 16.6%
    - mOS: NR vs. 26.8 months
    - DOR: 5.2 months vs. 2.1 months

- **CheckMate 141 Study Design**
  - Randomized, global, phase 3 trial
  - Key Eligibility Criteria:
    - R/M SCCHN
    - No active CNS metastases
    - Documentation of p16 to determine
    - Progression on or within 6 months of
    - R/M SCCHN of the oral cavity, pharynx, or larynx
    - HPV status
  - Key Assignments:
    - Nivolumab
      - 3 mg/kg IV q2w
    - Investigator’s Choice
  - Key Sample Size:
    - Planned sample size of 360 patients
    - Interim analysis after 195 events
    - 90% power for a hazard ratio of nivolumab to investigator’s choice
    - Total of 278 deaths required for analysis
  - KeyEndpoints:
    - ORR
    - mOS
    - DOR
  - KeyStatistical Plan:
    - Two-sided test procedure with one interim analysis
    - 2:1 randomization
  - Key Results:
    - ORR: 30.2% vs. 10.0%
    - mOS: NR vs. 12.6 months
    - DOR: 5.2 months vs. 2.1 months

- **CheckMate 141**
  - Key Differences:
    - ORR: 30.2% vs. 10.0%
    - mOS: NR vs. 12.6 months
    - DOR: 5.2 months vs. 2.1 months
  - Key Findings:
    - Nivolumab showed significant improvement of OS
  - Key Conclusions:
    - Nivolumab is a promising treatment for R/M SCCHN

### Adverse Events of Special Interest

- **Around 50% of pts received 2 or more lines of chemotherapy for R/M HNSCC:** CheckMate-141 Nivolumab vs. Investigator’s Choice (IC)

### CheckMate 141 Study Design

- **Primary endpoint:**
  - OS
  - Improvement in OS
  - HR = 0.667
  - Two-sided test procedure with one interim analysis
  - Planned sample size of 360 patients
  - Interim analysis after 195 (70%) events
  - 90% power for a hazard ratio of nivolumab to investigator’s choice
  - Total of 278 deaths required to ensure
  - Planned sample size of 360 patients
  - Interim analysis after 195 (70%) events
  - 90% power for a hazard ratio of nivolumab to investigator’s choice
  - Total of 278 deaths required to ensure

- **Any Grade**
  - Deaths, n 2 0 0 1 0
  - Deaths, % 0 0 0 1 0

- **Grade 3–4**
  - Deaths, n 2 0 0 1 0
  - Deaths, % 0 0 0 1 0

### Summary of Anti-PD-1/PD-L1 for R/M HNSCC

- **ORR, %**
  - CheckMate 141: 30.2%
  - KEYNOTE-055: 16.6%

- **mOS, mos**
  - CheckMate 141: NR
  - KEYNOTE-055: 28.5–43.4 months

- **Deaths, n**
  - CheckMate 141: 28
  - KEYNOTE-055: 121
Immune related adverse events (irAEs)

- Skin toxicity
- Gastrointestinal toxicity
- Diabetes
- IBD-like colitis
- Pancreatitis
- Liver toxicity
- Endocrine disorder
- Hypothyroidism
- Adrenal insufficiency
- Hypophysitis
- Interstitial lung disease
- Neurological toxicity
- Encephalopathy
- Guillain-Barré syndrome
- Myasthenia Gravis

Treatment algorithm of irAEs

 Grade 1: symptomatic treatment, continue IO

 Grade 2:

- Symptomatic treatment
- Hold IO until recovery from irAEs
- In case of prolonged or recurrent Grade 2 irAEs

  - Treat as Grade 3 irAEs

 Grade 3 or more:

- Discontinuation
- PSL 1-2(-4) mg/kg

  - In PSL refractory case, consider additional treatment

  - Infliximab, MMF, IVlg

Conclusions

- Nivolumab exhibited survival benefit in platinum refractory R/M HNSCC for the first time
- Optimal biomarker remains to be defined
- Further development of immune check point inhibitors for
  - 1st line R/M HNSCC
  - Locally advanced HNSCC
  - Combination with radiation therapy
  - Virus related HNC: OPC and NPC
  - Combination with other immune check point inhibitors
- Proper management of irAEs is crucial for IO therapy

<table>
<thead>
<tr>
<th>irAEs</th>
<th>Nivolumab 10 mg/kg, q2wks</th>
<th>Pembrolizumab 10 mg/kg, q3wks</th>
<th>Clinical course of irAEs: Ipilimumab 10 mg/kg</th>
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<tbody>
<tr>
<td>Skin toxicity</td>
<td>14 0 14 0 25 0.4</td>
<td>14 0 14 0 25 0.4</td>
<td>47-88 0-4</td>
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<td>Rash</td>
<td>15 0 13 0 15 0.8</td>
<td>15 0 13 0 15 0.8</td>
<td>28-80 0-4</td>
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<tr>
<td>Gastrointestinal toxicity</td>
<td>19 2 44 9 33 6</td>
<td>21 1 45 8 21 0.6</td>
<td>31-46 8-23 3</td>
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<tr>
<td>Diarrhea</td>
<td>1 0.6 12 8 12 9</td>
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<td>17 2 4 2.5 13 7</td>
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<tr>
<td>ALT increased</td>
<td>17 2 44 9 33 6</td>
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<td>Pulmonary toxicity</td>
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<tr>
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<td>3-9 3-7 1-5</td>
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- Clinical course of irAEs: Ipilimumab 10 mg/kg

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