Immunotherapy for Esophageal and Gastric Cancer

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Disclosures

• Ad-board: Celegen, Merck, Pfizer, Takeda, Taiho, Astra-Zeneca

• Honorarium: Celegen, Merck, Taiho

• Research grant: Celegen
Learning Objectives

• The Rationale for Immune checkpoints Inhibitor (ICI) and predictive factors for response

• The role of ICI through different lines of treatment
Rationale for PD1/PDL1 inhibition in gastric cancer

<table>
<thead>
<tr>
<th>PD-L1 expression (TC or IC)</th>
<th>42-65%\textsuperscript{1,2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of tumour-infiltrating lymphocytes (TILs)</td>
<td>Yes\textsuperscript{2}</td>
</tr>
<tr>
<td>PD-L1 as negative prognostic factor</td>
<td>Yes\textsuperscript{2,3}</td>
</tr>
</tbody>
</table>

PEMBROLIZUMAB FOR ALL MSI-H SOLID TUMORS

ORR (57%) for MSI-H gastric cancers in KEYNOTE-059 study

Dung T Le et at Science 2017
Fuchs CS et al Jama Oncol 2018
RESPONSE TO PEMBROLIZUMAB ACCORDING TO MSI AND EBV
PDL CPS >10 MORE COMMON IN EBV+/MSI-H TUMORS

- **EBV+**
  - CPS <1: 7%
  - CPS 1-9: 44%
  - CPS 10+: 49%

- **MSI-H**
  - CPS <1: 15%
  - CPS 1-9: 22%
  - CPS 10+: 63%

- **EBV-/MSS**
  - CPS <1: 2%
  - CPS 1-9: 58%
  - CPS 10+: 35%

- **All**
  - CPS <1: 29%
  - CPS 1-9: 36%
  - CPS 10+: 35%

Cho ESMO 2019
Clinical Outcome Prediction by ctDNA

Kim et al. Nature Medicine 2018
ATTRACTION 2: Nivolumab improves OS vs placebo ≥ 3rd line unselected by PD-L1

Overall Survival

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>Events, n</th>
<th>Median OS [95% CI], months</th>
<th>12-Month OS Rate [95% CI], %</th>
</tr>
</thead>
</table>

Hazard ratio, 0.63 (95% CI, 0.50–0.78)
P < 0.0001

Kang et al. Lancet 2017
KEYNOTE-061: Second-line Pembrolizumab (GEJ and Gastric Ca)
Overall Survival by PD-L1 CPS (Neg trial BUT)
CPS ≥10 is a unique population (19% of pts)

HR 0.64, 95% CI 0.41-1.02
Median OS (95% CI) 12 mos OS.
Pembro 10.4 mo (5.9-17.3) 45%
Paclitaxel 8.0 mo (5.1-9.9) 25%

Shitara et al. Lancet 2018
**KN-061: OS, PFS, ORR, and DOR for MSI-H Tumors**

**OS**

<table>
<thead>
<tr>
<th></th>
<th>Events/ Pts</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>6/15</td>
<td>0.42 (0.13-1.31)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>10/12</td>
<td></td>
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</tbody>
</table>

**PFS**

<table>
<thead>
<tr>
<th></th>
<th>Events/ Pts</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>8/15</td>
<td>0.54 (0.19-1.54)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>10/12</td>
<td></td>
</tr>
</tbody>
</table>

**ORR and DOR**

<table>
<thead>
<tr>
<th>Responses</th>
<th>ORR, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>46.7% (21.3-73.4)</td>
</tr>
<tr>
<td>2</td>
<td>16.7% (2.1-48.4)</td>
</tr>
</tbody>
</table>

**Median (95% CI)**

<table>
<thead>
<tr>
<th>Pembrolizumab</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>PFS</td>
</tr>
<tr>
<td>NR (5.6 mo-NR)</td>
<td>17.8 mo (2.7-NR)</td>
</tr>
<tr>
<td>8.1 mo (2.0-16.7)</td>
<td>3.5 mo (2.0-9.8)</td>
</tr>
</tbody>
</table>

**No. at risk**

<table>
<thead>
<tr>
<th>Pembrolizumab</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
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<tr>
<td>0</td>
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</tbody>
</table>

**DOR, mo median (range)**

<table>
<thead>
<tr>
<th>Pembrolizumab</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.5 to 26.0+</td>
<td>2.2 to 12.2+</td>
</tr>
</tbody>
</table>

Shitara K, et al. ESMO-GI (WCGC), 2018
KEYNOTE-181: Second-line Pembrolizumab (Esophageal Ca) Overall Survival by PD-L1 CPS (Neg trial BUT) CPS ≥10 is a unique population (35% of patients)

<table>
<thead>
<tr>
<th>Histology</th>
<th>n deaths/N pts</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous</td>
<td>139/167</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>51/55</td>
<td></td>
</tr>
</tbody>
</table>

Kojima, GI ASCO 2019
KEYNOTE-062 Study Design (NCT02494583)

Key Eligibility Criteria
- Locally advanced, unresectable or metastatic gastric or gastroesophageal adenocarcinoma
- HER2/neu negative, PD-L1-positive disease (CPS ≥1)
- ECOG PS 0 or 1

Stratification Factors
- Region\(^a\)
- Locally advanced or metastatic disease
- 5-FU or Capecitabine

N = 763
R (1:1:1)
N = 257
N = 250

Pembrolizumab 200 mg Q3W
for up to 35 cycles\(^b\)

Pembrolizumab 200 mg Q3W
(to 35 cycles) +
Chemotherapy\(^c\)

Placebo +
Chemotherapy

Until unacceptable toxicity, disease progression, or patient/physician withdrawal decision

Primary endpoints: OS and PFS
Secondary endpoints: ORR, Safety

\(^a\)EU/North America/Australia, Asia (South Korea, Hong Kong, Taiwan, Japan), Rest of World (including South America).

\(^b\)Administration of pembrolizumab monotherapy was not blinded.

\(^c\)Chemotherapy: Cisplatin 80 mg/m\(^2\) Q3W + 5-FU 800 mg/m\(^2\)/d for 5 days Q3W or capcitabine BID d1-14 Q3W (Cisplatin may be capped at 6 cycles as per country guidelines).

Presented By Josep Tabernero at 2019 ASCO Annual Meeting
Overall Survival: P vs C (CPS ≥1)

HR: 0.91
95% CI: 0.69-1.18

Overall Survival: P vs C (CPS ≥10)

HR: 0.69
95% CI: 0.49-0.97

Overall Survival: P+C vs C (CPS ≥1)

HR: 0.85
95% CI: 0.70-1.03

Overall Survival: P+C vs C (CPS ≥10)

HR: 0.85
95% CI: 0.62-1.17

CPS ≥ 1

CPS ≥ 10

MSI-H in KN-062

Pembro vs. C

Pembro+C vs. C

CPS ≥1

Events HR (95% CI)

Pembro 36% 0.29
Chemo 79% (0.11-0.81)

24-mo rate

71% 26%

12-mo rate

79% 47%

CPS ≥10

Events HR (95% CI)

Pembro 27% 0.21
Chemo 80% (0.06-0.83)

24-mo rate

82% 30%

12-mo rate

82% 50%

CPS ≥1

Events HR (95% CI)

Pembro + Chemo 35% 0.37
Chemo 79% (0.14-0.97)

24-mo rate

65% 26%

12-mo rate

71% 47%

CPS ≥10

Events HR (95% CI)

Pembro + Chemo 27% 0.26
Chemo 80% (0.07-0.99)

24-mo rate

82% 30%

12-mo rate

82% 50%

Median (95% CI)

NR (3.8-NR)
8.5 mo (5.3-20.8)

NR (10.7-NR)
13.6 mo (3.8-25.8)
Why didn’t chemo + pembrolizumab improve survival in gastric cancer?

Presented By Ian Chau at 2019 ASCO Annual Meeting

- Chemotherapy + PD (L) 1 antibody
- Chemo backbone
- Gastric cancer not optimal for combination
- Biomarker still not right
- Trial design – multiplicity

Tabernero et al ASCO 2019
ATTRACTION-3

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 210)</th>
<th>Chemotherapy (n = 209)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo</td>
<td>10.9</td>
<td>8.4</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(9.2–13.3)</td>
<td>(7.2–9.9)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.77 (0.62–0.96)</td>
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<tr>
<td>P value</td>
<td>0.019</td>
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</table>

Nivolumab provided superior OS, with a 23% reduction in the risk of death and a 2.5-month improvement in median OS, versus chemotherapy.

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Chemotherapy</th>
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<tbody>
<tr>
<td></td>
<td>210</td>
<td>209</td>
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<tr>
<td>Months</td>
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</table>

Unresectable advanced or recurrent SCC oesophagus Refractory to or intolerant to 1 prior line platinum + FP therapy

R

n=209

Taxane (docetaxel or paclitaxel)

n=210

Nivolumab 240 mg every 2 weeks

ATTRACTION-3

Cho et al ESMO19

*Intent-to-treat population; †Minimum follow-up: 17.6 months.
CI, confidence interval; mo, months.
ATRACTION-4 and CheckMate-649

Ongoing Phase 3 Trials of Nivolumab

ONO-4538-37
ATTRACTION-04
NCT02746796

CheckMate-649
NCT02872116

Primary Endpoints: PFS and OS
(any PD-L1)

Primary Endpoint: PFS and OS
(PD-L1+ve, ≥ CPS 5%)
LA/metastatic SCC OESOPHAGUS

**CHECKMATE 648**
- n=939
- Cisplatin + 5-FU
- Nivolumab + Cisplatin + 5-FU
- Nivolumab + ipilimumab

1° endpoint: OS and PFS in PD-L1 TPS ≥1
NCT03143153

**KEYNOTE 590**
- n=700
- Cisplatin + 5-FU
- Cisplatin + 5-FU + pembrolizumab

1° endpoint: OS and PFS in PD-L1 CPS ≥10
NCT03189719
Take Home message

- Immunotherapy new promising option for GEJ and gastric cancer patients
  
  Patients most likely to benefit:
  
  - EBV+ (5%), MSI-H (5-20%), high PDL expressors (CPS>10)
  
  - ctDNA, TMB role to be better defined
  
  - Minimal activity in unselected patients

- Less toxic with durable response compared to chemotherapy

- First line trials results awaited

- Role in non-metastatic disease?