IMMUNOTHERAPY FOR GASTRIC CANCER
ESMO Gastric Cancer Preceptorship Valencia 2019

Elizabeth Smyth, MD
Cambridge University NHS Foundation Trust
DISCLOSURES

- Astellas
- Servier
- Celgene
- BMS
- Five Prime Therapeutics
- Gritstone Oncology
TALK OUTLINE

- Immunotherapy biology
- Chemorefractory GC studies
- 2nd line GC studies
- 1st line GC studies
- Combinations
- Biomarkers
PRINCIPLES OF IMMUNOTHERAPY

Antigen presenting
Can you generate cytotoxic T-cells?

T-cell trafficking
Can the T-cells get to the tumour?

Peptide-MHC recognition
Can the T-cells see the tumour?

PD-L1 on tumour/inhibitory cytokines
Can the T-cells be deactivated?

 BLOCKADE OF PD-1 OR CTLA-4 SIGNALLING

- Anti-CTLA4 antibodies (ipilimumab, tremelimumab) block a negative regulatory signal during T-cell priming
- Anti-PD-1 antibodies (pembrolizumab, nivolumab) block the negative regulatory signal of PD-1 which is expressed on T-cells during long term antigen exposure

TALK OUTLINE

- Immunotherapy biology
- Chemorefractory GC studies
- 2nd line GC studies
- 1st line GC studies
- Combinations
- Biomarkers
IMMUNOTHERAPY IN CHEMOREFRACTORY GC

TAKE HOME MESSAGES

Anti-PD-1 therapy is superior to best supportive care in patient with chemorefractory GC (ATTRACTION 2)

Anti-PD-L1 therapy is not superior to chemotherapy in chemorefractory GC (JAVELIN300)
NIVOLUMAB IN CHEMOREFRACTORY GASTRIC CANCER
ATTRACTION-02

Key eligibility criteria:
- Unresectable advanced or recurrent gastric or gastroesophageal junction cancer
- Refractory to/intolerant of ≥2 standard therapy regimens
- ECOG PS of 0 or 1

Randomisation (2:1)

Nivolumab
3 mg/kg IV Q2W

Stratification: Country (Japan/South Korea/Taiwan), ECOG PS (0/1), organs with metastases (<2/≥2)

Placebo

Endpoints
Primary: OS
Secondary: PFS, BOR, ORR, TTR, DOR, DCR, safety
Exploratory: Efficacy by tumour PD-L1 expression

Patient Characteristics

<table>
<thead>
<tr>
<th>ECOG</th>
<th>0 vs. 1</th>
<th>29% vs. 71%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of disease</td>
<td>Gastric vs. other</td>
<td>82% vs. 18%</td>
</tr>
<tr>
<td>Prior regimens</td>
<td>2 vs. 3 vs. ≥4</td>
<td>20% vs. 40% vs. 40%</td>
</tr>
</tbody>
</table>
NIVOLUMAB IN CHEMOREFRACTORY GASTRIC CANCER

ATTRACTION-02: response rates and duration

ORR 12%

MEDIAN TIME TO RESPONSE WAS 1.6m (1.4-7.0m)
MEDIAN DURATION OF RESPONSE IN 9.8 MONTHS

RECIST response rates 12%
(but more patients have non-RECIST response)

NIVOLUMAB IN CHEMOREFRACTORY GASTRIC CANCER

ATTRACTION-02: updated survival results

Median follow-up: 15.7 months (range: 12.1–27.2)

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (N = 330)</th>
<th>Placebo (N = 163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>5.3 (4.6–6.4)</td>
<td>4.1 (3.4–4.9)</td>
</tr>
<tr>
<td>Hazard ratio:</td>
<td>0.62 (95% CI, 0.50–0.76)</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>

Hazard ratio: 0.62 (95% CI, 0.50–0.76) P<0.0001

Nivolumab led to a 38% reduction in the risk of death compared to BSC
NIVOLUMAB IN CHEMOREFRACTORY GASTRIC CANCER

ATTRACTION-02: survival appears to be independent of PD-L1 status

**PD-L1 <1%**

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (N=114)</th>
<th>Placebo (N=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo</td>
<td>6.1 (4.8–8.6)</td>
<td>4.2 (3.0–6.9)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.71 (95% CI, 0.50–1.01)</td>
<td></td>
</tr>
</tbody>
</table>

**PD-L1 ≥1%**

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (N=16)</th>
<th>Placebo (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo</td>
<td>5.2 (2.8–9.4)</td>
<td>3.8 (0.8–5.0)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.58 (95% CI, 0.24–1.38)</td>
<td></td>
</tr>
</tbody>
</table>

PD-L1 testing was retrospective: 14% tested population were PD-L1 positive

PD-L1 antibody 28-8 pharmDx assay: PD-L1 positivity was defined as staining in 1% or more of **tumour cells**.
**PEMBROLIZUMAB IN CHEMOREFRACTORY GASTRIC CANCER**

**KEYNOTE-059**

**Key eligibility criteria**
- Pts with recurrent or metastatic gastric or GEJ adenocarcinoma
- ECOG PS 0/1
- HER2/neu negative*
- No prior PD-1/PD-L1 tx

**Phase II non-randomised trial**

**Endpoints**
- Primary: ORR, safety
- Secondary: DoR, PFS, OS

**Cohort 1**
- ≥ 2 prior lines chemotherapy
- Pembrolizumab 200 mg Q3W

**Cohort 2**
- Treatment naïve
- Pembrolizumab 200 mg Q3W + Cisplatin 80 mg/m² Q3W + 5-FU 800 mg/m² Q3W or Capecitabine 1000 mg/m² BID Q3W

**Cohort 3**
- Treatment naïve PD-L1+
- Pembrolizumab 200 mg Q3W

Treatment until PD, 24m or intolerable toxicity, or withdrawal of consent

PEMBROLIZUMAB IN CHEMOREFRACTORY GASTRIC CANCER
KEYNOTE-059

Pts with recurrent or metastatic gastric or GEJ; ECOG PS 0/1; no prior PD-1/PD-L1

Cohort 1
≥ 2 prior lines chemotherapy

Pembrolizumab 200 mg Q3W

Treatment until PD, 24m or, intolerable toxicity, or withdrawal of consent

Patient Characteristics (N=259)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, yrs (range)</strong></td>
<td>62 (24-89)</td>
</tr>
<tr>
<td><strong>Geographic region, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>US vs. East Asia vs. Other</td>
<td>48% vs. 13% vs. 39%</td>
</tr>
<tr>
<td><strong>ECOG PS</strong></td>
<td></td>
</tr>
<tr>
<td>0 vs. 1</td>
<td>41% vs. 58%</td>
</tr>
<tr>
<td><strong>Tumour site (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Gastric vs. GOJ</td>
<td>48% vs. 51%</td>
</tr>
<tr>
<td><strong>Prior therapies</strong></td>
<td></td>
</tr>
<tr>
<td>2 vs. 3 vs. ≥4</td>
<td>52% vs. 29% vs. 19%</td>
</tr>
</tbody>
</table>
PEMBROLIZUMAB IN CHEMOREFRACTORY GASTRIC CANCER
KEYNOTE-059


*Included pts with measurable disease at BL and ≥ 1 post-BL assessment (n = 223).

ORR 11.6%
9% in MSS

Majority of responses are early

Median duration of response:
- All patients 8.4m
- PD-L1 positive 16.3m
- PD-L1 negative 6.9m

RECIST response rates are modest (identical to nivolumab in ATTRACTION-02)
# PEMBROLIZUMAB IN CHEMOREFRACTORY GASTRIC CANCER

**KEYNOTE-059**: ORR according to PD-L1 status and line of Tx

<table>
<thead>
<tr>
<th>ORR (%)</th>
<th>PD-L1 status</th>
<th>Line of Treatment</th>
<th>PD-L1 and 3rd Line</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive (n = 148)</td>
<td>Negative (n = 109)</td>
<td>3rd (n = 134)</td>
</tr>
<tr>
<td></td>
<td>15.5 (10.1-22.4)</td>
<td>6.4 (2.6-12.8)</td>
<td>16.4 (10.6-23.8)</td>
</tr>
</tbody>
</table>

Response rates ↑ PD-L1 positive vs. PD-L1 negative (15.5% vs 6.4%)

PD-L1 assay is 22C3 antibody using **CPS score**.
CPS score = (number positive cells (IC, tumour)/tumour cells) x 100
PD-L1 positive if ≥1%
ANTI-PD-1 THERAPY IN CHEMOREFRACTORY GC

Licensing status

Following ATTRACTION-2 and KEYNOTE 059 nivolumab and pembrolizumab were licensed in Asia and the US respectively for chemorefractory GC.

Because ATTRACTION-2 was conducted solely in Asian patients, the European Medicines Organisation has not granted a license to nivolumab in Europe.
**AVELUMAB IN CHEMOREFRACTORY GC**

**Javelin 300**

If anti-P1 therapy is superior to best supportive care in chemorefractory GC, can anti-PD-L1 therapy be superior to chemotherapy?

**Phase 3 JAVELIN Gastric 300 study design**

- **Patients with unresectable, recurrent, locally advanced or metastatic GC/GEJC whose disease has progressed on 2 prior regimens, unselected for PD-L1 expression**
  - Target enrollment: N=330

- **R 1:1**
  - Stratification: Asia vs non-Asia

- **Avelumab 10 mg/kg Q2W + BSC**

- **BSC + physician’s choice of chemotherapy (or BSC alone if ineligible for chemotherapy)**

- **Primary endpoint:** OS
  - Secondary endpoints: PFS, ORR, safety, PROs/QoL

- Treatment until confirmed disease progression, unacceptable toxicity, or withdrawal

AVELUMAB IN CHEMOREFRACTORY GC
Javelin 300

No benefit for avelumab compared to chemotherapy in overall survival

PFS benefit favours chemotherapy

ORR to chemotherapy and avelumab were both low (2-4%)
TALK OUTLINE

- Immunotherapy biology
- Chemorefractory GC studies
- 2nd line GC studies
- 1st line GC studies
- Combinations
- Biomarkers
IMMUNOTHERAPY IN 2L GASTRIC CANCER

TAKE HOME MESSAGES

- Anti-PD-1 therapy is not superior to chemotherapy in 2L PD-L1 negative or PD-L1 CPS ≥1 GC (KEYNOTE 061)

- Anti-PD-1 therapy is superior to chemotherapy in 2L high PD-L1 expressing (CPS ≥ 10) oesophageal cancer (KEYNOTE 181) (influenced by histology and geography)

- Anti-PD-1 therapy is superior to chemotherapy in 2L PD-L1 unselected squamous oesophageal cancer (in Asia) (ATTRACTION-3)
PEMBROLIZUMAB VS PAACLITAXEL IN 2L GC PATIENTS
KEYNOTE-061

Key eligibility criteria

- Adenocarcinoma of the stomach or GEJ that was metastatic or locally advanced but unresectable
- PD per RECIST v1.1 after first-line platinum- and fluoropyrimidine-containing therapy
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
  - First 489 patients: any PD-L1 CPS
  - Final 103 patients: PD-L1 CPS ≥1

Stratification factors

- Region (Eur/Israel/N America/Australia vs Asia vs rest of the world)
- ECOG PS (0 vs 1)
- TTP on first-line therapy (<6 mo vs ≥6 mo)
- PD-L1 CPS (<1 vs ≥1)

Endpoints

Primary: OS and PFS in the CPS ≥1 population

Critical analysis – paclitaxel + ramucirumab not used as comparator.
PEMBROLIZUMAB VS PACLITAXEL IN 2L GC PATIENTS
KEYNOTE-061: OS in CPS ≥1 population


<table>
<thead>
<tr>
<th>Events, n</th>
<th>Pembrolizumab</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>0.82 (0.66–1.03)</td>
<td>-</td>
</tr>
<tr>
<td>P-value</td>
<td>0.04205</td>
<td></td>
</tr>
</tbody>
</table>

Overall survival, %

No. at Risk

Crossing curves means violation of the proportional hazards assumption
Small number of patients at the tail of the curve
PEMBROLIZUMAB VS PACLITAXEL IN 2L GC PATIENTS
KEYNOTE-061: Progression free survival in CPS ≥1

Most patients in both arms progress at an early stage, but more common with pembrolizumab.

PEMBROLIZUMAB VS PACLITAXEL IN 2L GC PATIENTS

KEYNOTE-061: OS in different CPS populations and MSI-H

CPS < 1

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>1.20 (0.89–1.63)</td>
<td></td>
</tr>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>4.8 (3.9–6.1)</td>
<td>8.2 (6.8–10.6)</td>
</tr>
</tbody>
</table>

CPS ≥ 10

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>0.64 (0.41–1.02)</td>
<td></td>
</tr>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>10.4 (5.9–17.3)</td>
<td>8.0 (5.1–9.9)</td>
</tr>
</tbody>
</table>

CPS ≥ 10

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>Not reached</td>
<td>8.1 (2-16.7)</td>
</tr>
</tbody>
</table>

Pembrolizumab detrimental in PD-L1 negative

Pembrolizumab better than chemotherapy in sensitive populations

2L ANTI-PD-1 IN OESOPHAGEAL CANCER
KEYNOTE 181

Pembrolizumab 200 mg IV Q3W for up to 35 cycles

Investigator’s choice of 1 of the following:
Paclitaxel 80-100 mg/m² on days 1, 8, 15 Q4W
Docetaxel 75 mg/m² Q3W
Irinotecan 180 mg/m² Q2W

<table>
<thead>
<tr>
<th>Characteristic, n</th>
<th>Pembrolizumab N=314</th>
<th>Chemotherapy N=314</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range) ≥65 years</td>
<td>63 (23–84) 139 (44.3)</td>
<td>62 (24–84) 133 (42.4)</td>
</tr>
<tr>
<td>Male</td>
<td>273 (86.9)</td>
<td>271 (86.3)</td>
</tr>
<tr>
<td>Asia</td>
<td>121 (38.5)</td>
<td>122 (38.9)</td>
</tr>
<tr>
<td>Rest of World</td>
<td>193 (61.5)</td>
<td>192 (61.1)</td>
</tr>
<tr>
<td>ECOG PS 1</td>
<td>187 (59.6)</td>
<td>197 (62.7)</td>
</tr>
<tr>
<td>Squamous-cell carcinoma</td>
<td>198 (63.1)</td>
<td>203 (64.6)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>116 (36.9)</td>
<td>111 (35.4)</td>
</tr>
<tr>
<td>PD-L1 CPS ≥10</td>
<td>107 (34.1)</td>
<td>115 (36.6)</td>
</tr>
</tbody>
</table>

Baseline characteristics (ITT population)

Co-primary endpoints
OS in ITT
OS in SCC (n=401)
OS in CPS ≥ 10 (n = 222)
2L ANTI-PD-1 IN OESOPHAGEAL CANCER

KEYNOTE 181: Overall Survival (SCC)

<table>
<thead>
<tr>
<th>Events, n</th>
<th>Pembrolizumab</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR(a) (95% CI)</td>
<td>0.78 (0.63–0.96)</td>
<td>-</td>
</tr>
<tr>
<td>Median, mo (95% CI)</td>
<td>8.2 (6.7–10.3)</td>
<td>7.1 (6.1–8.2)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.0095(a)</td>
<td></td>
</tr>
</tbody>
</table>

Co-primary endpoints OS in
ITT negative
OS in SCC (n=401) negative
OS in CPS ≥ 10 (n = 222)

Not significant based on pre-specified statistical boundaries of \(P \leq 0.0077\) for superiority of OS in SCC

**2L Anti-PD-1 in Oesophageal Cancer**

**KEYNOTE 181: Overall Survival (PD-L1 CPS ≥10)**

Statistically significant benefit in terms of OS for CPS ≥ 10 patients meeting co-primary endpoint.
## 2L ANTI-PD-1 IN OESOPHAGEAL CANCER

**KEYNOTE 181: Overall Survival subgroup analysis**

### PD-L1 CPS ≥ 10

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of deaths/ No. of patients</th>
<th>Hazard ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>190/222</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>103/115</td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>87/107</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>161/191</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>29/31</td>
<td></td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>67/81</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>123/141</td>
<td></td>
</tr>
</tbody>
</table>

### Squamous-cell carcinoma

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of deaths/ No. of patients</th>
<th>Hazard ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>346/401</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>198/214</td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>148/167</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>290/337</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>56/64</td>
<td></td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>123/152</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>222/246</td>
<td></td>
</tr>
</tbody>
</table>

### Intent-to-Treat

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of deaths/ No. of patients</th>
<th>Hazard ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>553/628</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>329/356</td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>224/272</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>478/544</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>75/84</td>
<td></td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>198/242</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>353/384</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous-cell</td>
<td>346/401</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>207/227</td>
<td></td>
</tr>
<tr>
<td>PD-L1 CPS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td>139/167</td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>201/228</td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>194/231</td>
<td></td>
</tr>
<tr>
<td>Ex-Asia</td>
<td>152/170</td>
<td></td>
</tr>
</tbody>
</table>

Subgroup analysis reveals effect of histology and ethnicity even in high PD-L1 expressing tumours

FDA approval of pembrolizumab for 2L oesophageal squamous with CPS ≥ 10
2L ANTI-PD-1 IN OESOPHAGEAL CANCER
ATTRACTION-3 nivolumab in 2L OSCC in Asia

Key eligibility criteria
- Unresectable advanced or recurrent ESCC
- Refractory to or intolerant of 1 prior fluoropyrimidine/platinum-based therapy
- ECOG performance status 0 or 1

Nivolumab
240 mg IV Q2W

Docetaxel 75 mg/m² IV Q3W or paclitaxel 100 mg/m² IV QW × 6 weeks, then 1 week off

Primary endpoint:
- OS

Other key endpoints:
- PFS, ORR, DCR, TTR, DOR, HRQoL, and safety

R 1:1
Stratification:
- Region
- No. of organs with metastases
- PD-L1 expression

Kato et al, Lancet 2019
2L ANTI-PD-1 IN OESOPHAGEAL CANCER

ATTRACTION-3 nivolumab in 2L OSCC in Asia OS and PFS results

2.5 month benefit in median overall survival

Although median PFS favoured chemotherapy similar % of patients in each arm had 3L treatment

Kato et al, Lancet 2019
TALK OUTLINE

- Immunotherapy biology
- Chemorefractory GC studies
- 2nd line GC studies
- 1st line GC studies
- Combinations
- Biomarkers
Anti-PD-1 therapy is not inferior to chemotherapy in PD-L1 positive GC (KEYNOTE 062) – with caveats

Anti-PD-1 plus chemotherapy is not superior to chemotherapy alone in PD-L1 CPS ≥ 1 or 10 GC (KEYNOTE 062)
KEYNOTE 062
Chemotherapy vs chemo + pembro vs pembrolizumab in 1L PD-L1 CPS ≥1 GC

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

**Key Eligibility Criteria**

**Stratification Factors**
- Region³
- Locally advanced or metastatic disease
- 5-FU or Capecitabine

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

**Diagram:**
- Pembrolizumab 200 mg Q3W for up to 35 cycles
- Pembrolizumab 200 mg Q3W (to 35 cycles) + Chemotherapy
- Placebo + Chemotherapy
- Until unacceptable toxicity, disease progression, or patient/physician withdrawal decision

**Notes:**
³EU/North America/Australia, Asia (South Korea, Hong Kong, Taiwan, Japan), Rest of World (including South America).
⁴Administration of pembrolizumab monotherapy was not blinded.
⁵Chemotherapy: Cisplatin 80 mg/m² Q3W + 5-FU 800 mg/m²/d for 5 days Q3W or capecitabine BID d1-14 Q3W (Cisplatin may be capped at 6 cycles as per country guidelines).
# KEYNOTE 062

## Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>Pembro N = 256</th>
<th>Pembro + Chemo N = 257</th>
<th>Chemo N = 250</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>61.0 (20-83)</td>
<td>62.0 (22-83)</td>
<td>62.5 (23-87)</td>
</tr>
<tr>
<td>Male</td>
<td>180 (70)</td>
<td>195 (76)</td>
<td>179 (72)</td>
</tr>
<tr>
<td>ECOG PS 1</td>
<td>125 (49)</td>
<td>138 (54)</td>
<td>135 (54)</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>245 (96)</td>
<td>243 (95)</td>
<td>235 (94)</td>
</tr>
<tr>
<td>CPS ≥10</td>
<td>92 (36)</td>
<td>99 (39)</td>
<td>90 (36)</td>
</tr>
<tr>
<td>MSI-H</td>
<td>14 (5)</td>
<td>17 (7)</td>
<td>19 (8)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe/North America/Australia</td>
<td>148 (58)</td>
<td>148 (58)</td>
<td>147 (59)</td>
</tr>
<tr>
<td>Asia</td>
<td>62 (24)</td>
<td>64 (25)</td>
<td>61 (24)</td>
</tr>
<tr>
<td>Rest of World</td>
<td>46 (18)</td>
<td>45 (18)</td>
<td>42 (17)</td>
</tr>
<tr>
<td>Primary tumor location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>176 (69)</td>
<td>170 (66)</td>
<td>181 (72)</td>
</tr>
<tr>
<td>GEJ</td>
<td>79 (31)</td>
<td>85 (33)</td>
<td>67 (27)</td>
</tr>
<tr>
<td>Backbone therapy*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-FU</td>
<td>-</td>
<td>98 (38)</td>
<td>95 (38)</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>-</td>
<td>159 (62)</td>
<td>155 (62)</td>
</tr>
</tbody>
</table>

*Per stratification; Data cutoff: March 26, 2019.
KEYNOTE 062
Pembrolizumab vs chemotherapy in CPS ≥1 OS results

The non-inferiority margin was not crossed – therefore pembrolizumab can be declared non-inferior to chemotherapy in CPS ≥1 GC.

Tabernero et al, ASCO 2019
KEYNOTE 062
Pembrolizumab vs chemotherapy in CPS ≥10 OS results

CPS ≥10 patients results are encouraging but this is not a primary endpoint of the study

Tabernero et al, ASCO 2019
Most patients treated with pembrolizumab progress quickly regardless of CPS status

**KEYNOTE 062**  
Pembrolizumab vs chemotherapy in PFS results

**ORR**  
CPS ≥1  |  CPS ≥10  
--- | ---  
Pembro 15%  |  Chemo 37%  
Pembro 25%  |  Chemo 38%

---

**Events HR (95% CI)**

**CPS ≥1**
- Pembrolizumab 88%  
- Chemotherapy 89%  
- Events HR: 1.66  
- Median (95% CI): 2.0 mo (1.5-2.8)  
- 12-mo rate: 14%  
- Median (95% CI): 6.4 mo (5.7-7.0)  

**CPS ≥10**
- Pembrolizumab 80%  
- Chemotherapy 89%  
- Events HR: 1.10  
- Median (95% CI): 2.9 mo (1.6-5.4)  
- 12-mo rate: 21%  
- Median (95% CI): 6.1 mo (5.3-6.9)
KEYNOTE 062
Pembrolizumab plus chemotherapy vs chemotherapy OS results CPS ≥1

Pembrolizumab plus chemotherapy was not superior to chemotherapy alone

Tabernero et al, ASCO 2019
KEYNOTE 062
Pembrolizumab plus chemotherapy vs chemotherapy OS results CPS ≥10

Pembrolizumab plus chemotherapy was not superior to chemo alone in CPS ≥ 10 patients

?negative interaction between chemotherapy and effect of pembrolizumab in immunogenic tumours?

Tabernero et al, ASCO 2019
KEYNOTE 062
Pembrolizumab plus chemotherapy vs chemotherapy OS results CPS ≥10

Pembrolizumab plus chemotherapy was not superior to chemo alone in CPS ≥ 10 patients

?negative interaction between chemotherapy and effect of pembrolizumab in immunogenic tumours?
KEYNOTE 062
Pembrolizumab plus chemotherapy vs chemotherapy PFS results

Chemotherapy plus pembrolizumab equivalent PFS outcomes in CPS ≥1 and CPS ≥10 patients

Tabernero et al, ASCO 2019
KEYNOTE-062

Conclusions

In highly immunogenic tumours (CPS ≥10), pembrolizumab monotherapy is associated with a meaningful OS benefit compared to chemotherapy

..however even in this sensitive population, radiological response rates are low and median PFS is short

..not a treatment for symptomatic or rapidly progressing patients

….unknown effect of subsequent chemotherapy on outcomes – sequencing may be important

In highly immunogenic tumours (CPS ≥10), combination chemotherapy plus pembrolizumab modestly improved radiological response rates compared to chemotherapy, but did not improve overall survival

Full understanding of patient selection and other biomarkers is critical
TALK OUTLINE

- Immunotherapy biology
- Chemorefractory GC studies
- 2nd line GC studies
- 1st line GC studies
- Combinations
- Biomarkers
COMBINATION IMMUNOTHERAPY FOR GC

There are many, results are mostly preliminary

- Anti-CTLA4 plus anti-PD-1 (CHECKMATE 032)
- Anti-angiogenesis
  - Ramucirumab plus nivolumab/pembrolizumab
  - Regorafenib plus nivolumab
- HER2 targeting
  - Trastuzumab plus pembrolizumab plus 1L chemotherapy
  - Margetuxumab plus pembrolizumab 2L

Fukuoka et al, J Clin Oncol 37, 2019 (suppl; abstr 2522)
Janjigian, YY et al, J Clin Oncol 37, 2019 (suppl; abstr 4011)
Catenacci et al, J Clin Oncol 37, 2019 (suppl 4; abstr 65)
TALK OUTLINE

- Immunotherapy biology
- Chemorefractory GC studies
- 2nd line GC studies
- 1st line GC studies
- Combinations
- Biomarkers
HOW IMMUNOGENIC ARE GASTRIC AND OESOPHAGEAL CANCER?

TMB and PD-L1 expression across cancer types

- TMB and PD-L1 are independent predictors of likelihood of response to immune checkpoint blockade across tumour types.
- In gastric cancer and oesophageal cancer, a modest proportion of tumours are TMB-high or PD-L1 positive.
- Biomarker prevalence depends on the methodology of assessment.

BIOMARKERS FOR IMMUNE CHECKPOINT BLOCKADE IN GC: MSI, PD-L1, EBV

MSI
KEYNOTE-061

PD-L1 CPS >10
KEYNOTE-061 & KEYNOTE-062

MSI-H 2.4% mGC

EBV

# Immune Environment in a Heterogeneous Disease

<table>
<thead>
<tr>
<th>Subtype Characteristics</th>
<th>Immune Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CIN</strong></td>
<td></td>
</tr>
<tr>
<td>ERBB2 amplification</td>
<td></td>
</tr>
<tr>
<td>VEGFA amplification</td>
<td></td>
</tr>
<tr>
<td>TP53 mutation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Copy number changes:</td>
</tr>
<tr>
<td></td>
<td>Low immune score</td>
</tr>
<tr>
<td></td>
<td>Low IFNγ signature</td>
</tr>
<tr>
<td><strong>EBV</strong></td>
<td></td>
</tr>
<tr>
<td>EBV-CIMP</td>
<td></td>
</tr>
<tr>
<td>PIK3CA mutation</td>
<td></td>
</tr>
<tr>
<td>PD-L1/2 overexpression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rare in metastatic patients</td>
</tr>
<tr>
<td></td>
<td>PD-L1: tumour ++ TILs +++</td>
</tr>
<tr>
<td></td>
<td>High IFNγ signature</td>
</tr>
<tr>
<td><strong>MSI</strong></td>
<td></td>
</tr>
<tr>
<td>Hypermutation</td>
<td></td>
</tr>
<tr>
<td>Gastric CIMP</td>
<td></td>
</tr>
<tr>
<td>MLH1 silencing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rare in metastatic patients</td>
</tr>
<tr>
<td></td>
<td>PD-L1: tumour ++ TILs ++</td>
</tr>
<tr>
<td></td>
<td>High IFNγ signature</td>
</tr>
<tr>
<td><strong>GS</strong></td>
<td></td>
</tr>
<tr>
<td>Diffuse histology</td>
<td></td>
</tr>
<tr>
<td>CDH1, RHOA mutations</td>
<td></td>
</tr>
<tr>
<td>CLDN18-ARHGAP fusions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Genomically bland</td>
</tr>
<tr>
<td></td>
<td>Diffuse type rarely PD-L1+</td>
</tr>
<tr>
<td></td>
<td>Subsets may have TIL</td>
</tr>
</tbody>
</table>

Immunotherapy for gastroesophageal cancer

Conclusions

- **3L+:** Anti-PD-1 therapy is a validated standard for patients with chemorefractory gastroesophageal cancer; anti-PD-L1 not superior to chemotherapy. No license in Europe.

- **2L:** Nivolumab improved survival for previously treated SCC in Asia independent of PD-L1 status, pembrolizumab is licensed for 2L SCC with CPS ≥10 in the USA. No license in Europe.

- **1L:** Meaningful OS benefit for pembrolizumab high PD-L1 expressors (CPS≥10) in KEYNOTE 062 but more research needed.

- MSI is a robust predictor of anti-PD-1 benefit, all patients should be tested. PD-L1 variable depending on where measured (immune cells vs tumour) and antibody.

- Most GC patients do not benefit from immune checkpoint blockade monotherapy, combinations are needed to improve outcomes.