Immunotherapy in Gastric Cancer

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Shiraz University Of Medical Science
IMMUNE ENVIRONMENT IN A HETEROGENEOUS DISEASE

<table>
<thead>
<tr>
<th>Subtype characteristics</th>
<th>Immune characteristics</th>
</tr>
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<tbody>
<tr>
<td><strong>CIN</strong></td>
<td>Copy number changes:</td>
</tr>
<tr>
<td>ERBB2 amplification</td>
<td>Low immune score</td>
</tr>
<tr>
<td>VEGFA amplification</td>
<td>Low IFNγ signature</td>
</tr>
<tr>
<td>TP53 mutation</td>
<td></td>
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<tr>
<td><strong>EBV</strong></td>
<td>Rare in metastatic patients</td>
</tr>
<tr>
<td>EBV-CIMP</td>
<td>PD-L1:</td>
</tr>
<tr>
<td>PIK3CA mutation</td>
<td>tumour +++ TILs +++</td>
</tr>
<tr>
<td>PD-L1/2 overexpression</td>
<td>High IFNγ signature</td>
</tr>
<tr>
<td><strong>MSI</strong></td>
<td>Rare in metastatic patients</td>
</tr>
<tr>
<td>Hypermutation</td>
<td>PD-L1:</td>
</tr>
<tr>
<td>Gastric CIMP</td>
<td>tumour ++ TILs ++</td>
</tr>
<tr>
<td>MLH1 silencing</td>
<td>High IFNγ signature</td>
</tr>
<tr>
<td><strong>GS</strong></td>
<td>Genomically bland</td>
</tr>
<tr>
<td>Diffuse histology</td>
<td>Diffuse type rarely PD-L1+</td>
</tr>
<tr>
<td>CDH1, RHOA mutations</td>
<td>Subsets may have TIL</td>
</tr>
<tr>
<td>CLDN18-ARHGAP fusions</td>
<td></td>
</tr>
<tr>
<td>Subtypes</td>
<td>EBV-positive</td>
</tr>
<tr>
<td>--------------------------</td>
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</tr>
<tr>
<td><strong>Frequency, %</strong></td>
<td>8.8</td>
</tr>
<tr>
<td><strong>Demographic</strong></td>
<td>Male patients (81%)</td>
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<td><strong>Histology</strong></td>
<td></td>
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<td><strong>Main location</strong></td>
<td>Fundus or body (62%)</td>
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<td><strong>Molecular alterations</strong></td>
<td>EBV-CIMP, PD-L1/2, JAK2 overexpression, Mutation in PIK3CA, ARID1A, and BCOR, CDKN2A silencing, Immune cell signaling, Rare TP53 mutations</td>
</tr>
<tr>
<td><strong>Potential targets</strong></td>
<td>PIK3CA, JAK2, and PD-L1/PD-L2</td>
</tr>
<tr>
<td><strong>Treatment reaction</strong></td>
<td></td>
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<tr>
<td><strong>Predictive</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Prognostic</strong></td>
<td>Yes</td>
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Rationale for PD1/PDL1 inhibition in gastric cancer

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

1. Data from [source1]
2. Data from [source2]
3. Data from [source3]
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
Third-line treatment

**ATTRACTION-2**
- Nivolumab
- BSC

**KEYNOTE-059**
- Pembrolizumab
- BSC

**Javelin-300**
- Avelumab
- Investigator’ choice
**NIVOLUMAB IN CHEMOREFRAC TORY 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
- 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>Characteristic</th>
<th>Nivolumab 29% vs. Placebo 71%</th>
<th>Nivolumab 82% vs. Placebo 18%</th>
<th>Nivolumab 20% vs. Placebo 40% vs. Placebo 40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0 vs. 1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Site of disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric vs. other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior regimens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 vs. 3 vs. ≥4</td>
<td></td>
<td></td>
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</tbody>
</table>
NIVOLUMAB IN CHEMOREFRACTORY GASTRIC CANCER

ATTRACTION-02: response rates and duration

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) P&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

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 (95% CI)</td>
<td>6.1 (4.8–8.6)</td>
<td>4.2 (3.0–6.9)</td>
</tr>
<tr>
<td>Hazard ratio: 0.71 (95% CI, 0.50–1.01)</td>
<td></td>
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</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 (95% CI)</td>
<td>5.2 (2.8–9.4)</td>
<td>3.8 (0.8–5.0)</td>
</tr>
<tr>
<td>Hazard ratio: 0.58 (95% CI, 0.24–1.38)</td>
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</tbody>
</table>

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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**.
Third-line treatment

ATTRACTION-2
- Nivolumab
- BSC

KEYNOTE-059
- Pembrolizumab
- BSC

Javelin-300
- Avelumab
- Investigator’s choice
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

<table>
<thead>
<tr>
<th>Patient Characteristics (N=259)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
<td>62 (24-89)</td>
</tr>
<tr>
<td>Geographic region, n (%)</td>
<td></td>
</tr>
<tr>
<td>US vs. East Asia vs. Other</td>
<td>48% vs. 13% vs. 39%</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
</tr>
<tr>
<td>0 vs. 1</td>
<td>41% vs. 58%</td>
</tr>
<tr>
<td>Tumour site (%)</td>
<td></td>
</tr>
<tr>
<td>Gastric vs. GOJ</td>
<td>48% vs. 51%</td>
</tr>
<tr>
<td>Prior therapies</td>
<td></td>
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<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

RECIST response rates are modest (identical to nivolumab in ATTRACTION-02)

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
# 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%)

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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%
Third-line treatment

ATTRACTION-2
- Nivolumab
- BSC

KEYNOTE-059
- Pembrolizumab
- BSC

Javelin-300
- Avelumab
- Investigator’ choice
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%)
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)
Second-line treatment

KEYNOTE-061
- Pembrolizumab
- Paclitaxel
PEMBROLIZUMAB VS PACLITAXEL 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></th>
<th>Pembrolizumab</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n</td>
<td>151</td>
<td>175</td>
</tr>
<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>
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</table>

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

<table>
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<tr>
<th>Treatment</th>
<th>No.</th>
<th>Median (95% CI)</th>
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<tbody>
<tr>
<td>Pembrolizumab</td>
<td>177</td>
<td>1.27 (1.03–1.57)</td>
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<tr>
<td>Paclitaxel</td>
<td>184</td>
<td>-</td>
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</table>

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>1.20 (0.89–1.63)</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>
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</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>0.64 (0.41–1.02)</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>

Pembrolizumab detrimental in PD-L1 negative

Pembrolizumab better than chemotherapy in sensitive populations

Shitara K. et al. Lancet 2018;39;
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)
First-line treatment:

KEYNOTE-062
- Pembrolizumab
- Pembrolizumab+CT
- CT

KEYNOTE-590
- Pembrolizumab+CT
- CT

Check-Mate-649
- Nivolumab+ CT
- CT

ATTRACTION-4:
- Nivolumab+ CT
- CT

KEYNOTE-811
- Pembrolizumab + trastuzumab + CT
- Trastuzumab + CT
Efficacy and Safety of Pembrolizumab or Pembrolizumab Plus Chemotherapy vs Chemotherapy Alone for Patients With First-line, Advanced Gastric Cancer The KEYNOTE-062 Phase 3 Randomized Clinical Trial

Kohel Shitara, MD; Eric Van Cutsem, MD; Yung-Jue Bang, MD; Charles Fuchs, MD; Lucjan Wywlicz, MD; Keun-Wook Lee, MD; Iveta Kudaba, MD; Marcelo Garrido, MD; Hyun Cheol Chung, MD; Jeeyun Lee, PhD; Hugo Raul Castro, MD; Wasat Mansoor, MD; Maria Ignaz Braghieri, MD; Nina Karaseva, MD; Christian Cagievic, MD; Luis Villanueva, MD; Eraz Goekkurt, MD; Hironaga Satake, MD; Peter Erzinger, MD; Maria Alzina, MD; Al Berenson, MD; Joseph Chao, MD; Andrew H. Ko, MD; Zev A. Wainberg, MD; Uma Khur, MS; Sukrut Shah, PhD; S. Peter Kang, MD; Josep Tabernero, MD, PhD, MSC

Key Points

**Question** What is the antitumor activity of pembrolizumab or pembrolizumab plus chemotherapy vs chemotherapy in patients with advanced gastric/gastroesophageal junction (G/GEJ) cancer and programmed cell death ligand 1 (PD-L1) combined positive score (CPS) of 1 or greater in the first-line setting?

**Findings** Among 763 patients with untreated, locally advanced/unresectable or metastatic G/GEJ cancer enrolled in the phase 3 KEYNOTE-062 randomized clinical trial, pembrolizumab was noninferior to chemotherapy for overall survival in patients with advanced G/GEJ cancer with PD-L1 CPS of 1 or greater, with patients receiving pembrolizumab experiencing fewer treatment-related adverse events.

**Meaning** Pembrolizumab had a favorable benefit-to-risk profile in patients with advanced G/GEJ cancer with PD-L1 CPS of 1 or greater, including in the first-line setting.
Figure 2. Kaplan-Meier Estimates of Overall Survival According to Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS)

A. PD-L1 CPS=1

HR, 0.91 (99% CI, 0.69-1.18); noninferiority margin = 1.2

No. at risk (No. censored)
Pembrolizumab 256 (0) 162 (0) 120 (0) 94 (0) 59 (0) 23 (25) 4 (44) 0 (55)
Chemotherapy 250 (0) 192 (0) 114 (0) 75 (0) 38 (0) 15 (18) 2 (29) 0 (32)

B. PD-L1 CPS≥10

HR, 0.69 (95% CI, 0.49-0.97)

No. at risk (No. censored)
Pembrolizumab 92 (0) 62 (0) 52 (0) 45 (0) 32 (0) 13 (13) 4 (22) 0 (31)
Chemotherapy 90 (0) 70 (0) 42 (0) 28 (0) 16 (0) 7 (8) 0 (13) 0 (31)

C. PD-L1 CPS=1

HR, 0.85 (95% CI, 0.70-1.03); P = .05

No. at risk (No. censored)
Pembrolizumab and chemotherapy 257 (0) 194 (0) 136 (0) 88 (0) 52 (0) 17 (23) 5 (44) 0 (50)
Chemotherapy 250 (0) 192 (0) 114 (0) 75 (0) 38 (0) 15 (18) 2 (29) 0 (32)

D. PD-L1 CPS≥10

HR, 0.85 (95% CI, 0.62-1.17); P = .16

No. at risk (No. censored)
Pembrolizumab and chemotherapy 99 (0) 74 (0) 50 (0) 35 (0) 21 (0) 7 (16) 3 (21) 0 (24)
Chemotherapy 90 (0) 70 (0) 42 (0) 28 (0) 16 (0) 7 (8) 0 (15) 0 (15)
Figure 3. Overall Survival in Patients With MSI-H Tumors and PD-L1 CPS of 1 or Greater

Kaplan-Meier estimates of overall survival in patients with microsatellite instability-high (MSI-H) tumors in the programmed cell death ligand 1 (PD-L1) combined positive score (CPS) of 1 or greater population for pembrolizumab (A) and pembrolizumab plus chemotherapy (B) vs chemotherapy. Analysis of overall survival in patients with MSI-H tumors was not adjusted for multiplicity.
KEYNOTE 062
Chemotherapy vs chemo + pembro vs pembrolizumab in 1L PD-L1 CPS ≥1 GC

**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
- Locally advanced or metastatic disease
- 5-FU or Capecitabine

**Trial Design**

1. **Randomization (R)**: 1:1:1
2. **Treatment Arms**:
   - Pembrolizumab 200 mg Q3W for up to 35 cycles
   - Pembrolizumab 200 mg Q3W (to 35 cycles) + Chemotherapy
   - Placebo + Chemotherapy

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

**Notes**:
- EU/North America/Australia, Asia (South Korea, Hong Kong, Taiwan, Japan), Rest of World (including South America).
- Administration of pembrolizumab monotherapy was not blinded.
- Chemotherapy: 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>
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<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(^a)</td>
<td></td>
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<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>

\(^a\) Stratification; Data cutoff: March 26, 2019.
KEYNOTE 062
Pembrolizumab vs chemotherapy in CPS ≥1 OS results

No. at Risk

<table>
<thead>
<tr>
<th>Time, months</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
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</table>

Events | HR (99.2% CI) | N°a |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>79%</td>
<td>0.91</td>
</tr>
<tr>
<td>Chemo</td>
<td>86%</td>
<td>(0.69-1.18)</td>
</tr>
</tbody>
</table>

12-mo rate
47%
46%

24-mo rate
27%
19%

Median (95% CI)b
10.6 mo (7.7-13.8)
11.1 mo (9.2-12.8)

\textsuperscript{a} Non-inferiority margin; \textsuperscript{b} HR (95% CI) = 0.91 (0.74-1.10), \( P = 0.162 \) for superiority of P vs C; Data cutoff: March 26, 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
KEYNOTE 062
Pembrolizumab vs chemotherapy in PFS results

CPS ≥1
- Events HR (95% CI)
  - Pembrolizumab: 88% (1.66)
  - Chemo: 89% (1.37-2.01)

CPS ≥10
- Events HR (95% CI)
  - Pembrolizumab: 80% (1.10)
  - Chemo: 89% (0.79-1.51)

Most patients treated with pembrolizumab progress quickly regardless of CPS status.
KEYNOTE 062
Pembrolizumab plus chemotherapy vs chemotherapy OS results CPS ≥1

- **Events**: Pembro + Chemo 80% vs Chemo 86%
- **HR (95% CI)**: Pembro + Chemo 0.85 (0.70-1.03) vs Chemo
- **P**: Pembro + Chemo 0.046 vs Chemo

- **12-mo rate**: Pembro + Chemo 53% vs Chemo 46%
- **24-mo rate**: Pembro + Chemo 24% vs Chemo 19%

**Median (95% CI)**:
- Pembro + Chemo: 12.5 mo (10.8-13.9)
- Chemo: 11.1 mo (9.2-12.8)

**No. at Risk**:

<table>
<thead>
<tr>
<th>Time, months</th>
<th>Pembro + Chemo</th>
<th>Chemo</th>
</tr>
</thead>
<tbody>
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<td>229</td>
<td>194</td>
</tr>
<tr>
<td>42</td>
<td>229</td>
<td>194</td>
</tr>
</tbody>
</table>

Pembrolizumab plus chemotherapy was not superior to chemotherapy alone
KEYNOTE 062
Pembrolizumab plus chemotherapy vs chemotherapy OS results CPS ≥10

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + Chemo</td>
<td>76%</td>
<td>0.85</td>
<td>0.158</td>
</tr>
<tr>
<td>Chemo</td>
<td>83%</td>
<td>(0.62-1.17)</td>
<td></td>
</tr>
</tbody>
</table>

12-mo rate: 51% Pembro + Chemo, 47% Chemo
24-mo rate: 28% Pembro + Chemo, 22% Chemo

Median (95% CI): 12.3 mo (9.5-14.8) Pembro + Chemo, 10.8 mo (8.5-13.8) Chemo

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

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

<table>
<thead>
<tr>
<th>ORR</th>
<th>CPS ≥1</th>
<th>CPS ≥10</th>
</tr>
</thead>
<tbody>
<tr>
<td>P + chemo</td>
<td>49%</td>
<td>53%</td>
</tr>
<tr>
<td>Chemo</td>
<td>37%</td>
<td>38%</td>
</tr>
</tbody>
</table>

Chemotherapy plus pembrolizumab equivalent PFS outcomes in CPS ≥1 and CPS ≥10 patients
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.
First-line treatment:

**KEYNOTE-062**
- Pembrolizumab
- Pembrolizumab+CT
- CT

**KEYNOTE-590**
- Pembrolizumab+CT
- CT

**Check-Mate-649**
- Nivolumab+ CT
- CT

**ATTRACTION-4:**
- Nivolumab+ CT
- CT

**KEYNOTE-811**
- Pembrolizumab + trastuzumab + CT
- Trastuzumab + CT
CheckMate 649: Study Design

- International, randomized, open-label phase III trial
  - Stratified by PD-L1 (≥1% vs <1%), region (Asia vs US/Canada vs rest of world), ECOG PS (0 vs 1), CT (XELOX vs FOLFOX)

- Patients with previously untreated, unresectable advanced or metastatic gastric cancer, GEJ, or esophageal adenocarcinoma; not known to be HER2 positive; ECOG PS 0/1 (N = 1581)

- Current analysis
  - Nivolumab 360 mg + XELOX Q3W or Nivolumab 240 mg + FOLFOX Q2W (n = 789)
  - XELOX Q3W or FOLFOX Q2W (n = 792)
  - Nivolumab + Ipilimumab Q3W x 4 followed by Nivolumab 240 mg Q2W

- Until PD (treatment beyond PD permitted for nivolumab + CT), unacceptable toxicity, consent withdrawal, or end of study

- Coprimary endpoints: OS and PFS in patients with PD-L1 CPS ≥5
- Secondary endpoints: OS and PFS in all randomized patients and patients with PD-L1 CPS ≥10 and ≥ 1, BICR-assessed ORR
CheckMate 649: Overall OS and PFS

<table>
<thead>
<tr>
<th>Nivo + CT</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 789)</td>
<td>(n = 792)</td>
</tr>
</tbody>
</table>

**Median OS**
- Nivo + CT: 13.8 (12.6-14.6)
- CT: 11.6 (10.9-12.5)
- HR 0.80 (99.3% CI 0.68-0.94); *P* = .0002

**Median PFS**
- Nivo + CT: 7.7 (7.1-8.5)
- CT: 6.9 (6.6-7.1)
- HR 0.77 (95% CI 0.68-0.87)

- **Minimum follow-up:** 12.1 mo
- **Nivolumab + CT** increased OS vs CT in most prespecified subgroups

Janjigian. Lancet. 2021;[Epub].
# CheckMate 649: Overall Response

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nivolumab + CT (n = 603)</th>
<th>CT (n = 608)</th>
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<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>58 (54-62)</td>
<td>46 (42-50)</td>
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<tr>
<td>Best overall response, %</td>
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<td></td>
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<tr>
<td>CR</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>PR</td>
<td>48</td>
<td>40</td>
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<td>SD</td>
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<td>PD</td>
<td>7</td>
<td>10</td>
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<tr>
<td>NE</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Median TTR, mo (range)</td>
<td>1.5 (0.8-10.9)</td>
<td>1.5 (0.6-7.1)</td>
</tr>
<tr>
<td>Median DoR, mo (95% CI)</td>
<td>8.5 (7.2-9.9)</td>
<td>6.9 (5.8-7.2)</td>
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### CheckMate 649: Subgroup Analysis by PD-L1 CPS

<table>
<thead>
<tr>
<th>PD-L1 CPS*</th>
<th>n</th>
<th>Median, Mo</th>
<th>Unstratified HR†</th>
<th>ORR, %</th>
<th>Unweighted Difference in ORR, %</th>
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<tr>
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<td>Nivolumab + CT</td>
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</tr>
<tr>
<td>OS (overall)</td>
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<td>11.6</td>
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<td>&lt;1</td>
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<td>13.1</td>
<td>12.5</td>
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<tr>
<td>≥1</td>
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<td>606</td>
<td>12.4</td>
<td>12.3</td>
<td>0.94</td>
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<td>955</td>
<td>14.4</td>
<td>11.1</td>
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<tr>
<td>PFS (overall)</td>
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<td>6.9</td>
<td>0.77</td>
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<td>8.7</td>
<td>8.1</td>
<td>0.93</td>
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<td>6.9</td>
<td>0.75</td>
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<tr>
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<td>6.1</td>
<td>0.69</td>
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<table>
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<th>PD-L1 CPS†</th>
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<th>CT</th>
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<td>Overall</td>
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<td>58</td>
<td>46</td>
<td>12</td>
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<td>&lt;1</td>
<td>178</td>
<td>51</td>
<td>41</td>
<td>9</td>
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<tr>
<td>≥1</td>
<td>1019</td>
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<td>13</td>
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<tr>
<td>≥5</td>
<td>769</td>
<td>60</td>
<td>45</td>
<td>15</td>
</tr>
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</table>

*PD-L1 CPS expression was intermediate, unevaluable, or unavailable for 20 patients. †Unstratified HR for death or progression to death
†Randomized patients with target lesion at baseline. PD-L1 CPS expression was intermediate, unevaluable, or unavailable for 14 patients.

- Survival benefit with nivolumab + CT was enriched at higher PD-L1 CPS cutoffs
- ORR benefit of nivolumab + CT vs CT was consistent across all assessed subgroups

CheckMate 649: TRAEs With Potential Immunologic
Cause in Patients Treated With Nivolumab + CT

<table>
<thead>
<tr>
<th>Select TRAEs</th>
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<tbody>
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<td></td>
<td>Any Grade, n (%)</td>
<td>Grade 3/4, n (%)</td>
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<td>Endocrine</td>
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<td>5 (&lt;1)</td>
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<tr>
<td>Gastrointestinal</td>
<td>262 (34)</td>
<td>43 (5)</td>
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<tr>
<td>Hepatic</td>
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<td>29 (4)</td>
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<tr>
<td>Pulmonary</td>
<td>40 (5)</td>
<td>14 (2)</td>
</tr>
<tr>
<td>Renal</td>
<td>26 (3)</td>
<td>6 (&lt;1)</td>
</tr>
<tr>
<td>Skin</td>
<td>214 (27)</td>
<td>26 (3)</td>
</tr>
</tbody>
</table>
CheckMate 649: Time to Symptom Deterioration and Patient QoL

- Most patients in both treatment arms reported being “not at all” or “a little” bothered by treatment adverse events (FACT-Ga GP5 questionnaire)

- Adding nivolumab to CT did not cause patients to be more bothered by treatment adverse events

CheckMate 649: Conclusions

- In the phase III CheckMate 649 trial in untreated patients with advanced gastroesophageal cancers, nivolumab + CT significantly prolonged OS and PFS in all treated patients and in patients with PD-L1 CPS ≥5
  - Median OS, all treated patients: 13.8 vs 11.6 mo (HR: 0.80; \( P = .0002 \)); median PFS: 7.7 vs 6.9 mo (HR: 0.77)

- Treatment-related AEs with potential immunologic cause occurred in ≤5% per site at grade 3/4 severity; most cases resolved with standard management

- Investigators concluded that data support nivolumab + CT as standard first-line treatment for patients with advanced non-HER2+ gastroesophageal cancers

MORE PEOPLE WERE ALIVE ON OPDIVO + CHEMOTHERAPY* COMPARED TO CHEMOTHERAPY* ALONE

Patients with PD-L1 CPS ≥5 (n=955)

PEOPLE ALIVE AT 1 YEAR

57% compared to 46% on OPDIVO + chemotherapy* compared to on chemotherapy* alone

OPDIVO + chemotherapy* proven to lower the risk of dying by 29%

compared to chemotherapy* alone

Half of the patients who were on OPDIVO + chemotherapy* were alive at 14.4 months compared to half being alive on chemotherapy* alone at 11.1 months

All patients regardless of PD-L1 CPS status (n=1,581)

PEOPLE ALIVE AT 1 YEAR

55% compared to 48% on OPDIVO + chemotherapy* compared to on chemotherapy* alone

OPDIVO + chemotherapy* proven to lower the risk of dying by 20%

compared to chemotherapy* alone

Half of the patients who were on OPDIVO + chemotherapy* were alive at 13.8 months compared to half being alive on chemotherapy* alone at 11.6 months
For patients with PD-L1 biomarker CPS ≥5, half of the patients on **OPDIVO + chemotherapy** went 7.7 months without their cancer spreading, growing, or getting worse compared to half who went without their cancer spreading, growing, or getting worse on **chemotherapy** alone at 6.0 months.

**OPDIVO + chemotherapy** reduced the risk of cancer spreading, growing, or getting worse by 32% compared to **chemotherapy** alone.

*Modified FOLFOX-6 (leucovorin, fluorouracil, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).*
794 PATIENTS who had received chemoradiation followed by surgery to remove their esophageal or GEJ cancer.

532 patients were assigned to receive OPDIVO.

262 patients were assigned to receive a placebo.

Clinical Trial Results:
Patients taking OPDIVO lived without their cancer returning 2x longer than patients on placebo.

At 22.4 months, half of the patients on OPDIVO remained free of esophageal or GEJ cancer returning.

At 11 months, half of the patients on placebo remained free of esophageal or GEJ cancer returning.

31% REDUCED RISK of esophageal or GEJ cancer returning after chemoradiation followed by surgery compared to placebo.
First-line treatment:

**KEYNOTE-062**
- Pembrolizumab
- Pembrolizumab + CT
- CT

**KEYNOTE-590**
- Pembrolizumab + CT
- CT

**Check-Mate-649**
- Nivolumab + CT
- CT

**ATTRACTION-4:**
- Nivolumab + CT
- CT

**KEYNOTE-811**
- Pembrolizumab + trastuzumab + CT
- Trastuzumab + CT
PFS was significantly improved in N+C vs. C, achieving the primary objective. The combination of nivolumab and chemotherapy, which demonstrated clinically meaningful efficacy in PFS and ORR with a manageable safety profile but not statistically significant improvement in OS, can be considered a new first-line treatment option in advanced or recurrent G/GEJ cancer.
Key eligibility criteria
- Treatment-naïve patients
- Unresectable advanced or recurrent HER2-negative gastric or gastroesophageal junction cancer
- ECOG PS of 0 or 1
- Neoadjuvant or adjuvant chemotherapy allowed if completed ≥180 days prior to recurrence

Randomization 1:1

Nivolumab 360 mg IV Q3W + SOX

Treatment continued until
- Progressive disease per RECIST v1.1
- Unacceptable toxicity
- Withdrawal of consent

Nivolumab 360 mg IV Q3W + CapeOX

*IV oxaliplatin 130 mg/m² on day 1 followed by 20 days off and oral S-1 or oral capecitabine twice daily for 14 days followed by 7 days off. S-1 initial dose was 40 mg/m²/dose. Capecitabine initial dose was 1,000 mg/m²/dose.
ECOG PS = Eastern Cooperative Oncology Group performance status; IV = intravenous; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors
**Study Design**

Phase 3 part of ATTRACTION 4 is a double blind, randomized controlled study conducted at 130 centers in Japan, Korea, and Taiwan.

**Key eligibility criteria:**
- Unresectable advanced or recurrent HER2 (-) G/GEJ cancer
- ECOG PS of 0-1
- Chemo naïve
- Neoadjuvant or adjuvant chemotherapy allowed if completed ≥180 days prior to recurrence

**Treatment continued until:**
- Progressive disease per RECIST v1.1
- Unacceptable toxicity
- Withdrawal of consent

**Co-primary endpoints:**
- PFS (central assessment by IRRC) and OS

**Other key endpoints:**
- PFS (investigator’s assessment), ORR, DOR, DCR, TTR, BOR, and safety

---

- Nivolumab 360 mg IV Q3W + SOX\(^b\) or CapeOX\(^c\) therapy
- Placebo + SOX\(^b\) or CapeOX\(^c\) therapy

---

- At data cutoff for interim analysis of PFS (31 Oct 2018), the median follow up period was 11.6 months
- At data cutoff for final analysis of OS (31 Jan 2020), the median follow up period was 26.6 months
- A total of 724 patients were randomized between Mar 2017 and May 2018

---

\(a\) ClinicalTrials.gov identifier: NCT02420790,

\(b\) SOX: 5-fluorouracil calcium folinate (5-fluorouracil) 400 mg/m² orally twice daily (days 1-14) and Oxaliplatin 130 mg/m² IV (day 1), q3w

\(c\) CapeOX: CapeOX: 1000 mg/m² orally twice daily (days 1-14) and Oxaliplatin 130 mg/m² IV (day 1), q3w
<table>
<thead>
<tr>
<th></th>
<th>Nivolumab plus chemotherapy</th>
<th>Chemotherapy alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>10.45 MONTHS</td>
<td>8.34 MONTHS</td>
</tr>
<tr>
<td>OS</td>
<td>17.45 MONTHS</td>
<td>17.15 MONTHS</td>
</tr>
</tbody>
</table>
First-line treatment:

KEYNOTE-062
- Pembrolizumab
- Pembrolizumab + CT
- CT

KEYNOTE-590
- Pembrolizumab + CT
- CT

Check-Mate-649
- Nivolumab + CT
- CT

ATTRACTION-4:
- Nivolumab + CT
- CT

KEYNOTE-811
- Pembrolizumab + trastuzumab + CT
- Trastuzumab + CT
KEYNOTE-811 Interim Analysis: Study Design

- Randomized, double-blind, placebo-controlled phase III study
  - Stratified by geographic region,
  - PD-L1 CPS, chemotherapy choice

- Patients with HER2+ advanced gastric or GEJ adenocarcinoma, no prior therapy in advanced setting (N = 692)

- Pembrolizumab 200 mg IV Q3W + Trastuzumab 6 mg/kg IV Q3W + FP or CAPOX*

- Placebo IV Q3W + Trastuzumab 6 mg/kg IV Q3W + FP or CAPOX*

- Up to 35 cycles or until disease progression, unacceptable toxicity, or study withdrawal

- Efficacy analysis: first 264 patients enrolled; safety analysis: 433 patients who received ≥1 dose of study medication

- **Primary endpoints:** OS, PFS per RECIST v1.1 by BICR

- **Secondary endpoints:** ORR and DoR per RECIST v1.1 by BICR, safety

### KEYNOTE-811 Interim Analysis: Efficacy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Efficacy Population</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pembrolizumab (n = 133)</td>
<td>Placebo (n = 131)</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>74.4 (66.2-81.6)</td>
<td>51.9 (43.0-60.7)</td>
</tr>
<tr>
<td>ORR difference*</td>
<td>22.7 (11.2-33.7); P = .00006</td>
<td></td>
</tr>
<tr>
<td>DCR, % (95% CI)</td>
<td>96.2 (91.4-98.8)</td>
<td>89.3 (82.7-94.0)</td>
</tr>
<tr>
<td>Best response, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>15 (11)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>PR</td>
<td>84 (63)</td>
<td>64 (49)</td>
</tr>
<tr>
<td>SD</td>
<td>29 (22)</td>
<td>49 (37)</td>
</tr>
<tr>
<td>PD</td>
<td>5 (4)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>0</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Not assessed</td>
<td>0</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Duration of response*</td>
<td>(n = 99)</td>
<td>(n = 68)</td>
</tr>
<tr>
<td>Median, mo (range)</td>
<td>10.6 (1.1+ to 16.5+)</td>
<td>9.5 (1.4+ to 15.4+)</td>
</tr>
<tr>
<td>≥6 mo duration, %</td>
<td>70.3</td>
<td>61.4</td>
</tr>
<tr>
<td>≥9 mo duration, %</td>
<td>58.4</td>
<td>51.1</td>
</tr>
<tr>
<td>Size reduction from baseline, n (%)</td>
<td>(n = 124)</td>
<td>(n = 122)</td>
</tr>
<tr>
<td>Any decrease</td>
<td>97</td>
<td>90</td>
</tr>
<tr>
<td>≥80% decrease</td>
<td>32</td>
<td>15</td>
</tr>
</tbody>
</table>

*Calculated using Mietten and Numinen method; stratified by randomization stratification factors.

1Calculated in patients with measurable disease at baseline and at least 1 post baseline measurement.
KEYNOTE-811 Interim Analysis: Target Lesion Change From Baseline

<table>
<thead>
<tr>
<th></th>
<th>Pembro Arm</th>
<th>Placebo Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>124(^a)</td>
<td>122(^a)</td>
</tr>
<tr>
<td>Any decrease</td>
<td>97%</td>
<td>90%</td>
</tr>
<tr>
<td>Decrease ≥80%</td>
<td>32%</td>
<td>15%</td>
</tr>
</tbody>
</table>

- Adding pembrolizumab to trastuzumab/CT led to a 22.7% improvement in ORR vs placebo + trastuzumab/CT as first-line treatment for patients with advanced HER2+ gastric or gastroesophageal junction cancer.

- Responses with pembrolizumab + trastuzumab/CT were deeper and more durable than those achieved with placebo + trastuzumab/CT.

- Safety profile was similar between treatment arms with no unexpected safety concerns associated with pembrolizumab.

- Investigators suggest pembrolizumab + trastuzumab/chemotherapy may be a possible new treatment option for previously untreated, unresectable or metastatic HER2+ gastric or gastroesophageal junction cancer.
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)
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
Figure. Immunotherapy Trials in Gastric and Esophageal Cancer*

KEYNOTE-590 (ESCC, PD-L1 ≥ 10%)
Pembrolizumab + Chemo
improves OS/PFS vs. Chemo

CheckMate-649 (AC, PD-L1 ≥ 5%)
Nivolumab + Chemo
improves OS/PFS vs. Chemo

ATTRACTION-4 (G/GEJ AC)
Nivolumab + Chemo
improves PFS but not OS vs. Chemo

ATTRACTION-3 (ESCC)
Nivolumab improves OS vs. Taxanes

ATTRACTION-2
Nivolumab improves OS vs. Placebo, Approved in Japan

KEYNOTE-181 (ESCC, PD-L1 ≥ 10%)
Pembrolizumab improves OS vs. Chemo

KEYNOTE-059 (phase II)
Pembrolizumab is FDA approved for all patients receiving 3L+ therapy

KEYNOTE-062 (PD-L1+)
Pembrolizumab noninferior to Chemo

JAVELIN-100
Avelumab does not improve OS vs. Paclitaxel

KEYNOTE-061 (PD-L1+)
Pembrolizumab does not improve OS vs. Paclitaxel

JAVELIN-300
Avelumab does not improve OS vs. Chemo

First-Line

First-Line Maintenance

Second-Line

Third-Line+
Immunotherapy Advances Into the Adjuvant and First-line Metastatic Settings for Gastric and Esophageal Cancers

November 24, 2020

Combined chemo-immunotherapy should be the new standard-of-care frontline therapy for patients with gastric, GEJ, and esophageal cancers, both for adenocarcinoma and squamous cell carcinoma.
# Immunotherapy in gastric cancer treatment

**First-line treatment:**
- **KEYNOTE-062**
  - Pembrolizumab
  - Pembrolizumab + CT
  - CT
- **KEYNOTE-590**
  - Pembrolizumab + CT
  - CT
- **Check-Mate-649**
  - Nivolumab + CT
  - CT
- **ATTRACTION-4**
  - Nivolumab + CT
  - CT
- **KEYNOTE-811**
  - Pembrolizumab + trastuzumab + CT
  - Trastuzumab + CT

**Second-line treatment:**
- **KEYNOTE-061**
  - Pembrolizumab
  - Paclitaxel

**Third-line treatment:**
- **ATTRACTION-2**
  - Nivolumab
  - BSC
- **KEYNOTE-059**
  - Pembrolizumab
  - BSC
- **Javelin-300**
  - Avelumab
  - Investigator’s choice

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**Diagram:**
- **T Lymphocyte**
- **Cancer cell**
- Anti-PD-1
- Anti-PD-L1
- PD-1
- PD-L1
- TCR
- MHC
- B7
- Anti-CTLA-4
- CTLA-4
- CD28