New targets for metastatic gastric cancer

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Disclosures

- I have nothing to disclose for this presentation.
Beyond histological classification

Angiogenesis

Singapore

HK

- c-MET, FGFR, mTOR etc
- PD-1/PD-L1 inhibitor

TCGA

ACRG

Strategies of targeting cancer

1. Killing the proliferating cells

2. Enhance Immunity! (Cytokines/IFN, IL-2, vaccine, immune checkpoint inhibitor)

3. Angiogenesis inhibitor: (avastin, pazopanib, axitinib, cabozantinib)

4. GF RTK
   Herceptin, cetuximab, Glivec

5. Intracellular signaling
   (mTOR inhibitors, MEK inhibitors)

6. Targeting both
   (sunitinib, sorafenib)
Schematic view of targeted therapies in gastric cancer and sites of action

World J Gastroenterol. 2016 Jan 14;22(2):471-89
Phase III trials targeting HGF/c-Met pathway

**RILOMET-1**

Patients with MET+, unresectable metastatic or locally advanced gastric or GEJ cancer (Planned N = 450)

- Rilotumumab (AMG102) 15 mg/kg q21d + Epirubicin, Cisplatin, Capecitabine (ECX)
- Placebo q21d + Epirubicin, Cisplatin, Capecitabine (ECX)

- Primary endpoint: OS

**MetGastric**

Patients with MET+, HER2-negative, metastatic gastric or GEJ cancer (planned N = 800)

- Onartuzumab mFOLFOX6*
- Placebo mFOLFOX6*

- Primary endpoint: OS in MET 2+/3+ and ITT populations

ClinicalTrials.gov. NCT01697072 & NCT01662869
Rilotumumab and Onartuzumab as a 1\textsuperscript{st} line

RILOMET-1\textsuperscript{1}

METGastric\textsuperscript{2}

Both trials stopped prematurely

1. ASCO 2015 (abstr #4000); 2. JAMA Oncol. 2017;3:620-7
Why did MET blockage fail?

- MET overexpression might not be an appropriate target for MET blockage

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**RILOMET-1**

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>MET expression tertile</th>
<th>Subjects, n</th>
<th>Events, n</th>
<th>Median OS</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rilotumumab (n=304)</td>
<td>25~&lt;45%</td>
<td>95</td>
<td>43</td>
<td>10.2</td>
<td>7.2-12.4</td>
</tr>
<tr>
<td></td>
<td>45~&lt;80%</td>
<td>98</td>
<td>41</td>
<td>8.1</td>
<td>6.4-11.9</td>
</tr>
<tr>
<td></td>
<td>≥80%</td>
<td>110</td>
<td>44</td>
<td>10.7</td>
<td>7.2-15.9</td>
</tr>
<tr>
<td>Placebo (n=305)</td>
<td>25~&lt;45%</td>
<td>100</td>
<td>37</td>
<td>12.4</td>
<td>8.9-NE</td>
</tr>
<tr>
<td></td>
<td>45~&lt;80%</td>
<td>103</td>
<td>39</td>
<td>10.4</td>
<td>8.6-15.4</td>
</tr>
<tr>
<td></td>
<td>≥80%</td>
<td>102</td>
<td>31</td>
<td>11.1</td>
<td>9.5-NE</td>
</tr>
</tbody>
</table>

**METGastric**

<table>
<thead>
<tr>
<th>Characteristics MET IHC stratification levels</th>
<th>Total Patients, No.</th>
<th>Placebo (n = 283)</th>
<th>Onartuzumab (n = 279)</th>
<th>Hazard Ratio (95% Wald CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>92</td>
<td>46</td>
<td>46</td>
<td>0.82 (0.43-1.56)</td>
</tr>
<tr>
<td>II</td>
<td>122</td>
<td>63</td>
<td>59</td>
<td>0.70 (0.36-1.35)</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>&gt;999.99 (0.00-NE)</td>
</tr>
<tr>
<td>IV</td>
<td>271</td>
<td>136</td>
<td>135</td>
<td>0.92 (0.54-1.58)</td>
</tr>
<tr>
<td>V</td>
<td>75</td>
<td>37</td>
<td>38</td>
<td>1.93 (0.71-5.22)</td>
</tr>
</tbody>
</table>

1. ASCO 2015 (abstr #4000); 2. JAMA Oncol. 2017;3:620-7
FGFR2 Dysregulation is Linked to Shorter Survival in GC Patients

FGFR2 Gene Amplification

- FGFR2 non-amplified (n=29)
- FGFR2 amplified (n=14)

Follow-up (months)

Overall Survival

FGFR2 FISH: p = .012

Jung et al. 2009

FGFR2b Protein Over-Expression

- FGFR2b IHC neg (n=353)
- FGFR2b IHC pos (n=9)

Follow-up (months)

Overall Survival

p < 0.001

Han et al. 2015
SHINE study: AZD4547 vs. paclitaxel as a 2\textsuperscript{nd} line Tx

Bang YJ et al. ASCO 2015

GC
2\textsuperscript{nd}-line
FGFR2 polysomy or gene amplification (n=55)
High level FGFR2 amplification predicts response to AZD4547
## Summary of Initial Monotherapy Antitumor Activity of FPA144 in FGFR2b+ Gastric Patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>FPA144 Treated (N=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR * (95% CI)</td>
<td>33% (7%, 70%)</td>
</tr>
<tr>
<td>Best Objective Response (%)</td>
<td></td>
</tr>
<tr>
<td>Complete Response</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>3* (33%)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>2 (23%)</td>
</tr>
<tr>
<td>Disease Control Rate (95% CI)</td>
<td>77% (40%, 97%)</td>
</tr>
<tr>
<td>12-Week PFS (95% CI)</td>
<td>67% (30%, 93%)</td>
</tr>
<tr>
<td>Median Duration of Treatment, days (Range)</td>
<td>112 (42-182)</td>
</tr>
</tbody>
</table>

* Pooled across all dosing cohorts (1 at 6 mg/kg, 1 at 10 mg/kg and 1 at 15 mg/kg). All responses were confirmed (one after the data cutoff with the patient still on treatment). Investigator review was used for assessments. Data cutoff was April 1, 2016.

**Partial Response in Patient Treated with 6 mg/kg FPA144**

**Screening (Day -14)**

**Cycle 4 Day 1 (Day 83)**
DDR (DNA Damage Response) in GC

- HRD (Homologous Recombination Defect) leads to massive genome instability
- Genes of HR pathway are found to be deregulated in tumor
  - HRD as therapeutic target

BRCA1/2 Mutation, PALB2 mutation, RAD51B, RAD54B mutation, etc
**GOLD: Phase III study**

Patients with advanced gastric cancer* who progressed following first-line therapy (n=525)
- China (n=202)
- Japan (n=102)
- Korea (n=201)
- Taiwan (n=20)

1:1

**Olaparib** 100 mg tablet twice daily + weekly **paclitaxel** 80 mg/m² iv
N=263

**Placebo** + weekly **paclitaxel** 80 mg/m² iv
N=262

Paclitaxel treatment was on days 1, 8 and 15 of a 28-day cycle until progression,† unmanageable toxicity or consent withdrawal

- **Co-primary endpoint**
  - OS all patients (FAS‡)
  - OS for patients with an ATM protein-negative tumour§

**Secondary endpoints included:** PFS; ORR; HRQoL∥; safety and tolerability

**Study designed to detect HR=0.7 with a median OS improvement of 8.0–>11.4 months in the overall population, and HR=0.35 with a median OS improvement of 8.0–>22.9 months in the ATM protein-negative population**
- **Statistical significance was 0.025 (the Hochberg approach)**

*Including the gastro-oesophageal junction (GEJ); †Evaluated by RECIST 1.1; ‡adjusted for ATM status, country and gastrectomy status at baseline; §adjusted for country & gastrectomy status at baseline; ∥Assessed by the EORTC QLQ-C30 global HRQoL scale

**Bang YJ et al. ESMO 2016**
Overall survival in the FAS

FAS (n=525; 72.6% OS maturity)

Olaparib/paclitaxel Placebo/paclitaxel

Events: total patients (%) 181:263 (68.8) 200:262 (76.3)

Median OS, months 8.8 6.9

HR=0.79
97.5% CI (0.63, 1.00); \( P=0.0262^* \)

*Due to Hochberg's multiple testing procedure, statistical significance was \( P<0.025 \) for each population

Bang YJ et al. ESMO 2016
New agents in development

- New agents targeting known targets: Her-2, MET, FGFR, angiogenesis
- Ab-drug conjugates
- GS-5745 (MMP-9 inhibitor)
- Napabucasin (BBI608) – stemness inhibitor
- IMAB362: Anti-CLDN18.2 antibody
- Anetumab- targeting mesothelin
- CDK4/6 inhibitors
- Epigenetics modulators: BET inhibitor
- TGF-b inhibitor
- Etc …

- Immunotherapy

Proper patients selection: Precision Medicine
Role of Immune Therapy for GC?

YES!

- **Sep 22, 2017**
  - FDA Approves Merck’s Keytruda (pembrolizumab) for Previously Treated Patients with Recurrent Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Cancer Whose Tumors Express PD-L1 based on KEYNOTE-059 trial.
  - Japanese Ministry of Health, Labor and Welfare (MHLW) approved nivolumab (Opdivo) for the treatment of unresectable advanced or recurrent gastric cancer which has progressed after chemotherapy based on ATTRACTION-2 (ONO-4538-12) trial.
  - May 23 2017: Pem for MSI-H tumors
  - Aug 2017 Nivolumab for MSI-H CRC
Immunity is important in survival of esophagogastric cancer  
-> Potential applicability of immune therapies

- Immune cell (CD3, CD4+/CD8+ T-cell) infiltration showed a better survival

- PD-L1/2 positive, CD4(+)CD25_high/Treg positive patients have a poorer prognosis

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Estimate of Neoantigen Repertoire: potential immune therapy for GC

Somatic mutation frequencies (mutation burden) in “exomes” from 3,083 tumor–normal pairs
Current treatment of metastatic GC (median 16-18 months)

1st line Tx

90%
5-fluorouracil/platinum (+/- docetaxel) 5-7 Mo
+ Trastuzumab in Her-2 +

2nd line Tx

Pembrolizumab in PD-L1 +
Paclitaxel or Irinotecan (3-5 Mo)
+ Ramucirumab

Supportive

Nivolumab

Chemotherapy

Apatinib?

Presented

Tremelimumab monotherapy
Ipilimumab monotherapy (maintenance)
Pembrolizumab monotherapy (KN-12)
Avelumab monotherapy (Javelin 100)
Ipilimumab + Nivolumab combo (CM 032)
Nivolumab vs BSC (III, Attraction-2)

Ongoing

Avelumab vs SOC (III)
Atezolizumab/Durvalumab monotherapy
Durvalumab + Ramucirumab, Durvalumab + Tremelimumab

Pem/nivo + CTx(III)
Pembrolizumab vs Pac(III)
Ipilimumab + Nivolumab vs SOC (III)

* CTLA-4 targeting agents, PD-1/PD-L1 targeting agents
Tremelimumab (Phase II)

- 18 Western patients (6 GC, 6 GEJ, 6 Eso)
- 15mg/kg **every 90 days**
- 2\textsuperscript{nd} line (n=15), 3\textsuperscript{rd} line (n=3)
- RR 6%: 1 PR (Tx for 32.7 Mo), 4 SD
- TTP: 2.83 Mo (2.7 ~ 3.0)
- OS: 4.83 Mo (4.1 ~ 5.6)

**Treatment-related toxicities**

<table>
<thead>
<tr>
<th>Toxity</th>
<th>Grade</th>
<th>Cycle 1 (n=18)</th>
<th>Cycle 2 (n=6)</th>
<th>Cycle 3 (n=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itch</td>
<td>1</td>
<td>8</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>(pancolitis &amp; perforation*)</td>
<td>5*</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*0.6%: ipilimumab >3mg/kg

Ralph et al., Clin Cancer Res 2010
Randomized phase II study of ipilimumab vs. BSC following first line therapy

- Median iPFS (95% CI)
  - Ipilimumab: 2.9 months (1.6-5.2) vs BSC: 4.9 months (3.5-6.5)
  - No improvement in iPFS (HR=1.44: 80% CI 1.09-1.91, P=0.097)

- Overall survival Ipi: 12.7mo, BSC: 12.1mo (NS)

Keynote-012: pembrolizumab phase Ib

- 39 patients (19 East Asia, 20 ROW)
- Pembrolizumab 10mg/Kg every 2 weeks
- PD-L1 enriched: 22C3 pharmDx kit (Dako)
  - screen: 65/162 (40%) by prototype (tumor cell ≥ 1%)

- Mostly ≥ 3rd lines

<table>
<thead>
<tr>
<th>RR</th>
<th>PR 13 (33%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>1.9 Mo</td>
</tr>
<tr>
<td>OS</td>
<td>11.4 Mo</td>
</tr>
</tbody>
</table>

Bang et al. ASCO 2015
KEYNOTE-059: Efficacy and Safety of Pembrolizumab Alone or in Combination With Chemotherapy in Patients With Advanced Gastric or Gastroesophageal Cancer


1David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA, USA; 2Indiana University School of Medicine, Indianapolis, IN, USA; 3Aichi Cancer Center Hospital, Nagoya, Aichi, Japan; 4Mayo Clinic, Rochester, MN, USA; 5Pontificia Universidad Católica de Chile, Santiago, Chile; 6Sheba Medical Center and the Sackler School of Medicine, Tel Aviv, Israel; 7National Cancer Center East, Chiba, Japan; 8University of Chicago Medicine, Chicago, IL, USA; 9Tel Aviv-Sourasky Medical Center, Tel Aviv University, Tel Aviv, Israel; 10Memorial Sloan Kettering Cancer Center, New York, NY, USA; 11Sanford Health, Sioux Falls, SD, USA; 12Seoul National University Hospital, Seoul, Republic of Korea; 13Saitama Cancer Center, Saitama, Japan; 14Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; 15Merck & Co., Inc., Kenilworth, NJ, USA; 16Yale Cancer Center, New Haven, CT, USA
Cohort 1
≥2 prior lines of chemotherapy
PD-L1 positive or negative

Pembrolizumab
200 mg Q3W

Treat for up to 35 cycles (~2 years), or until progression or intolerable toxicity

Follow-up for survival by telephone until death, withdrawal, or study end

Cohort 2
No prior therapy
PD-L1 positive or negative

Pembrolizumab 200 mg Q3W +
Cisplatin 80 mg/m² Q3W +
5-FU 800 mg/m² Q3W or
Capecitabine 1000 mg/m² BID Q3W

Cohort 3
No prior therapy
PD-L1 positive

Pembrolizumab
200 mg Q3W

Response assessment per RECIST v1.1: First scan 9 weeks after cycle 1, then every 6 weeks for year 1 and every 9 weeks thereafter

Primary end points: Safety (all cohorts); ORR by central review per RECIST v1.1 (cohort 1: all patients and patients with PD-L1–positive expression); ORR by central review per RECIST v1.1 (cohort 3)

PD-L1 positive was defined as combined positive score (CPS) ≥1 (previously reported as and equivalent to CPS ≥1%), where CPS = the number of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells × 100

aCapecitabine was administered only in Japan.
bPD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA, USA).
Cohort 3
No prior therapy
PD-L1 positive

Pembrolizumab 200 mg Q3W

Treat for up to 35 cycles (~2 years), or until progression or intolerable toxicity

Follow-up for survival by telephone until death, withdrawal, or study end

Cohort 2
No prior therapy
PD-L1 positive or negative

Pembrolizumab 200 mg Q3W + Cisplatin 80 mg/m² Q3W + 5-FU 800 mg/m² Q3W or Capecitabine 1000 mg/m² BID Q3W

Cohort 1
≥2 prior lines of chemotherapy
PD-L1 positive or negative

Pembrolizumab 200 mg Q3W

1st line Tx
5-fluorouracil/platinum (+/- docetaxel) 5-7 Mo

Paclitaxel or Irinotecan (3-5 Mo)

Supportive
(3rd - 4th line Tx)
Salvage Chemotherapy

2nd line Tx
Paclitaxel or Irinotecan (3-5 Mo)

+ Ramucirumab

+ Trastuzumab in Her-2 +

aCapecitabine was administered only in Japan.
## Cohort 1: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 259</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>62 (24-89)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>198 (76)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>200 (77)</td>
</tr>
<tr>
<td>Asian</td>
<td>41 (16)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (3)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>107 (41)</td>
</tr>
<tr>
<td>1</td>
<td>151 (58)</td>
</tr>
<tr>
<td>No. of prior therapies, n (%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>134 (52)</td>
</tr>
<tr>
<td>3</td>
<td>75 (29)</td>
</tr>
<tr>
<td>≥4</td>
<td>50 (19)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 259</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of primary tumor, n (%)</td>
<td></td>
</tr>
<tr>
<td>GEJ</td>
<td>134 (52)</td>
</tr>
<tr>
<td>Gastric</td>
<td>124 (48)</td>
</tr>
<tr>
<td>Prior gastrectomy, n (%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>49 (19)</td>
</tr>
<tr>
<td>Partial</td>
<td>17 (7)</td>
</tr>
<tr>
<td>No</td>
<td>193 (75)</td>
</tr>
<tr>
<td>PD-L1 expression, n (%)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>148 (57)</td>
</tr>
<tr>
<td>Negative</td>
<td>109 (42)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1)</td>
</tr>
<tr>
<td>HER2 status, n (%)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>63 (24)</td>
</tr>
<tr>
<td>Negative</td>
<td>194 (75)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

Data cutoff: April 21, 2017.
## Cohort 1: Response

<table>
<thead>
<tr>
<th>Response</th>
<th>All Patients N = 259</th>
<th>PD-L1 Positive&lt;sup&gt;a&lt;/sup&gt; n = 148</th>
<th>PD-L1 Negative n = 109</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>95% CI</td>
<td>%</td>
</tr>
<tr>
<td>ORR</td>
<td>12</td>
<td>8-17</td>
<td>16</td>
</tr>
<tr>
<td>DCR&lt;sup&gt;c&lt;/sup&gt;</td>
<td>27</td>
<td>22-33</td>
<td>34</td>
</tr>
<tr>
<td>BOR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>3</td>
<td>1-6</td>
<td>3</td>
</tr>
<tr>
<td>PR</td>
<td>9</td>
<td>6-13</td>
<td>13</td>
</tr>
<tr>
<td>SD</td>
<td>16</td>
<td>12-21</td>
<td>18</td>
</tr>
<tr>
<td>PD</td>
<td>56</td>
<td>49-62</td>
<td>53</td>
</tr>
</tbody>
</table>

- Median (range) follow-up in cohort 1: 5.6 (0.5-24.7) months
- 134 patients received pembrolizumab as third-line therapy; ORR was 16%, and DCR was 31%
- 125 patients received pembrolizumab as fourth plus–line therapy; ORR was 7%, and DCR was 23%

<sup>a</sup>PD-L1 positive was defined as combined positive score (CPS) ≥1 (previously reported as and equivalent to CPS ≥1%), where CPS = ratio of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) to the total number of tumor cells × 100.
<sup>b</sup>Only confirmed responses were included.
<sup>c</sup>CR + PR + SD ≥2 months. Data cutoff: April 21, 2017.
Cohort 1: Best Percentage Change and Longitudinal Change in Target Lesion Size

**Best Percentage Change in All Patients (n = 224)**

- 95 patients (42%) experienced a reduction in target lesion size

**Longitudinal Change in Responders (n = 31)**

- Median (range) duration of response: 14.2 (2.4-19.4+) months

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**PD-L1 positive**

**PD-L1 expression unknown**

**PD-L1 negative**

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*a Only patients with measurable disease per RECIST v1.1 by central review at baseline who had ≥1 postbaseline assessment were included (n = 223); assessment was nonevaluable in 1 patient.

*b Longitudinal change in the sum of the longest target lesion diameters from baseline in responders (n = 31).

+No progressive disease at last disease assessment.

Data cutoff: April 21, 2017.
Cohort 1: PFS and OS in All Patients

### Progression-Free Survival (PFS)
- **Median (95% CI):** 2.0 (2.0-2.1) mo
- **6-mo rate:** 14.6%

### Overall Survival (OS)
- **Median (95% CI):** 5.5 (4.2-6.5) mo
- **6-mo rate:** 45.7%

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Data cutoff: April 21, 2017.
Cohort 1: PFS and OS by PD-L1 Expression

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (95% CI)</td>
<td>Median (95% CI)</td>
</tr>
<tr>
<td></td>
<td>6-mo rate</td>
<td>6-mo rate</td>
</tr>
<tr>
<td>PD-L1+</td>
<td>2.1 (2.0-2.1) mo</td>
<td>5.8 (4.4-7.8) mo</td>
</tr>
<tr>
<td></td>
<td>18.2%</td>
<td>48.4%</td>
</tr>
<tr>
<td>PD-L1−</td>
<td>2.0 (1.9-2.0) mo</td>
<td>4.6 (3.2-6.5) mo</td>
</tr>
<tr>
<td></td>
<td>9.9%</td>
<td>42.9%</td>
</tr>
</tbody>
</table>

**Progression-Free Survival, %**

**Overall Survival, %**

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>PD-L1+</th>
<th>PD-L1−</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 mo</td>
<td>148</td>
<td>109</td>
</tr>
<tr>
<td>2-4 mo</td>
<td>89</td>
<td>48</td>
</tr>
<tr>
<td>4-6 mo</td>
<td>39</td>
<td>16</td>
</tr>
<tr>
<td>6-8 mo</td>
<td>27</td>
<td>10</td>
</tr>
<tr>
<td>8-10 mo</td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td>10-12 mo</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>12-14 mo</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>14-16 mo</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>16-18 mo</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>18-20 mo</td>
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<td>0</td>
</tr>
<tr>
<td>20-22 mo</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>22-24 mo</td>
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</tr>
<tr>
<td>24-26 mo</td>
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**No. at risk**

<table>
<thead>
<tr>
<th></th>
<th>PD-L1+</th>
<th>PD-L1−</th>
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<tbody>
<tr>
<td>0-2 mo</td>
<td>148</td>
<td>109</td>
</tr>
<tr>
<td>2-4 mo</td>
<td>124</td>
<td>79</td>
</tr>
<tr>
<td>4-6 mo</td>
<td>92</td>
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<td>6-8 mo</td>
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<td>8-10 mo</td>
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<td>10-12 mo</td>
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<td>12-14 mo</td>
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<td>14-16 mo</td>
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<td>16-18 mo</td>
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<td>10</td>
<td>3</td>
</tr>
<tr>
<td>20-22 mo</td>
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<td>1</td>
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<tr>
<td>22-24 mo</td>
<td>1</td>
<td>1</td>
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<tr>
<td>24-26 mo</td>
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</tr>
</tbody>
</table>

FDA approved Pembrolizumab as of Sep. 22th 2017

Data cutoff: April 21, 2017.
KEYNOTE-059 Study Design

Cohort 1
≥2 prior lines of chemotherapy
PD-L1 positive or negative

Pembrolizumab
200 mg Q3W

Treat for up to 35 cycles (~2 years), or until progression or intolerable toxicity

Follow-up for survival by telephone until death, withdrawal, or study end

Cohort 2
No prior therapy
PD-L1 positive or negative

Pembrolizumab 200 mg Q3W +
Cisplatin 80 mg/m² Q3W +
5-FU 800 mg/m² Q3W or
Capecitabine 1000 mg/m² BID Q3W

Cohort 3
No prior therapy
PD-L1 positive

Pembrolizumab 200 mg Q3W

1st line Tx

5-fluorouracil/platinum
(+/- docetaxel) 5-7 Mo

2nd line Tx

Paclitaxel or
Irinotecan (3-5 Mo)

(3rd - 4th line Tx)

Salvage Chemotherapy

Supportive

+ Trastuzumab in Her-2 +

+ Ramucirumab
Cohort 2: Response

<table>
<thead>
<tr>
<th>Response</th>
<th>All Patients</th>
<th>PD-L1 Positive&lt;sup&gt;a&lt;/sup&gt;</th>
<th>PD-L1 Negative</th>
<th>N = 25</th>
<th>n = 16</th>
<th>n = 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>60 39-79</td>
<td>69 41-89</td>
<td>38 9-76</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCR&lt;sup&gt;c&lt;/sup&gt;</td>
<td>80 59-93</td>
<td>75 48-93</td>
<td>75 35-97</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BOR</td>
<td></td>
<td></td>
<td></td>
<td>CR</td>
<td>4 0-20</td>
<td>0 0-22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PR</td>
<td>56 35-76</td>
<td>69 41-89</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SD</td>
<td>32 15-54</td>
<td>19 4-48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PD</td>
<td>4 0-20</td>
<td>6 0-30</td>
</tr>
</tbody>
</table>

- Median (range) follow-up in cohort 2: 13.8 (1.8-24.1) months

<sup>a</sup>PD-L1 positive was defined as combined positive score (CPS) ≥1 (previously reported as and equivalent to CPS ≥1%), where CPS = number of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells × 100.

<sup>b</sup>Only confirmed responses were included.

<sup>c</sup>CR + PR + SD ≥6 months.

Data cutoff: April 21, 2017.
Cohort 2: Best Percentage Change and Longitudinal Change in Target Lesion Size

24 patients (96%) experienced a reduction in target lesion size.

Longitudinal change in the sum of the longest target lesion diameters from baseline in patients with ≥1 postbaseline assessment (n = 25).

+No progressive disease at last disease assessment.

Data cutoff: April 21, 2017.

Only patients with measurable disease per RECIST v1.1 by central review at baseline who had ≥1 postbaseline assessment were included (n = 25); assessment was nonevaluable for 1 patient.

Longitudinal change in the sum of the longest target lesion diameters from baseline in patients with ≥1 postbaseline assessment (n = 25).

Median (range) duration of response: 4.6 (2.6-20.3+) months.

Best Percentage Change in All Patients (n = 24)

Longitudinal Change in All Patients (n = 25)

PD-L1 positive
PD-L1 expression unknown
PD-L1 negative
Cohort 2: PFS and OS

**Progression-Free Survival (PFS)**

- **Median (95% CI):** 6.6 (5.9-10.6) months
- **6-mo rate:** 68.0%

**Overall Survival (OS)**

- **Median (95% CI):** 13.8 (8.6-NR) months
- **6-mo rate:** 76.0%

Data cutoff: April 21, 2017.
KEYNOTE-059 Study Design

**Cohort 1**
≥2 prior lines of chemotherapy
PD-L1 positive or negative

**Cohort 2**
No prior therapy
PD-L1 positive or negative

**Cohort 3**
No prior therapy
PD-L1 positive

---

**Pembrolizumab 200 mg Q3W**

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

Treat for up to 35 cycles (~2 years), or until progression or intolerable toxicity

Follow-up for survival by telephone until death, withdrawal, or study end

---

**1st line Tx**
5-fluorouracil/platinum
(+/- docetaxel) 5-7 Mo

**2nd line Tx**
Paclitaxel or Irinotecan (3-5 Mo)

**Supportive**
Salvage Chemotherapy

**(3rd - 4th line Tx)**

+ Trastuzumab in Her-2 +

+ Ramucirumab
## Cohort 3: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>62 (32-75)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>19 (61)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>16 (52)</td>
</tr>
<tr>
<td>Asian</td>
<td>15 (48)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>14 (45)</td>
</tr>
<tr>
<td>1</td>
<td>17 (55)</td>
</tr>
<tr>
<td>No. of prior therapies, n (%)</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of primary tumor, n (%)</td>
<td></td>
</tr>
<tr>
<td>GEJ</td>
<td>12 (39)</td>
</tr>
<tr>
<td>Gastric</td>
<td>19 (61)</td>
</tr>
<tr>
<td>Prior gastrectomy, n (%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>9 (29)</td>
</tr>
<tr>
<td>Partial</td>
<td>3 (10)</td>
</tr>
<tr>
<td>No</td>
<td>19 (61)</td>
</tr>
<tr>
<td>PD-L1 positive, n (%)</td>
<td>31 (100)</td>
</tr>
<tr>
<td>HER2 negative, n (%)</td>
<td>31 (100)</td>
</tr>
</tbody>
</table>

Data cutoff: April 21, 2017.
Cohort 3: Response

Median (range) follow-up: 17.5 (1.7-20.7) months

Only confirmed responses were included.

<table>
<thead>
<tr>
<th>Response</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>26</td>
<td>12-45</td>
</tr>
<tr>
<td>DCR(^b)</td>
<td>36</td>
<td>19-55</td>
</tr>
<tr>
<td>BOR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>7</td>
<td>1-21</td>
</tr>
<tr>
<td>PR</td>
<td>19</td>
<td>8-38</td>
</tr>
<tr>
<td>SD</td>
<td>29</td>
<td>14-48</td>
</tr>
<tr>
<td>PD</td>
<td>39</td>
<td>22-58</td>
</tr>
</tbody>
</table>

*Only confirmed responses were included.

\(^b\)CR + PR + SD ≥6 months.

Data cutoff: April 21, 2017.
Cohort 3: Best Percentage Change and Longitudinal Change in Target Lesion Size

24 patients (77%) experienced a reduction in target lesion size

Change From Baseline, %

-100 -80 -60 -40 -20 0 20 40 60 80 100

0 2 4 6 8 10 12 14 16 18 20 22 24

Time Since Treatment Initiation, months

Best Percentage Change in All Patients (n = 31)\(^a\)

Longitudinal Change in All Patients (n = 30)\(^b\)

Median (range) duration of response: 9.6 (2.1-17.8+) months

\(^a\)Only patients with measurable disease per RECIST v1.1 by central review at baseline who had ≥1 postbaseline assessment were included (n = 31) and assessments were nonevaluable/not available in 3 patients.

\(^b\)Longitudinal change in the sum of the longest target lesion diameters from baseline in patients with CR or PR (n = 30).

\(+\) No progressive disease at last disease assessment.

Data cutoff: April 21, 2017.
Cohort 3: PFS and OS

Progression-Free Survival, %

Overall Survival, %

**PFS**

<table>
<thead>
<tr>
<th>Median (95% CI)</th>
<th>6-mo rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3 (2.0-6.0) mo</td>
<td>34.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median (95% CI)</th>
<th>6-mo rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.7 (9.2-20.7) mo</td>
<td>72.9%</td>
</tr>
</tbody>
</table>

Data cutoff: April 21, 2017.
Summary and Conclusions

Updated KEYNOTE-059 results

• Pembrolizumab continues to demonstrate, in patients with advanced G/GEJ cancer,
  – Promising antitumor activity and durable response as monotherapy in patients whose
disease has progressed after ≥2 prior lines of therapy
  – Encouraging antitumor activity in combination with chemotherapy in previously
untreated patients
  – Encouraging antitumor activity as monotherapy in previously untreated patients with
PD-L1–positive tumors

• Responses were regardless of PD-L1 expression, but higher in patients with PD-L1–positive
tumors in cohorts 1 and 2

• Safety was manageable and consistent with that of previous reports: no new safety signals
Patients were permitted to continue treatment beyond initial RECIST v1.1–defined disease progression, as assessed by the investigator, if receiving clinical benefit and tolerating study drug.

Retrospective determination of tumor PD-L1 expression, defined as positive if staining in ≥1% (or ≥5%) of tumor cells, was performed in a central laboratory using immunohistochemistry (28-8 pharmDx assay) for patients with available tumor samples.
### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab N = 330</th>
<th>Placebo N = 163</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>62 (20–83)</td>
<td>61 (26–83)</td>
</tr>
<tr>
<td><strong>Male sex, n (%)</strong></td>
<td>229 (69)</td>
<td>119 (73)</td>
</tr>
<tr>
<td><strong>Country, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>152 (46)</td>
<td>74 (45)</td>
</tr>
<tr>
<td>South Korea</td>
<td>146 (44)</td>
<td>74 (45)</td>
</tr>
<tr>
<td>Taiwan</td>
<td>32 (10)</td>
<td>15 (9)</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>95 (29)</td>
<td>48 (29)</td>
</tr>
<tr>
<td>1</td>
<td>235 (71)</td>
<td>115 (71)</td>
</tr>
<tr>
<td><strong>Primary site of disease, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric(^a)</td>
<td>272 (82)</td>
<td>135 (83)</td>
</tr>
<tr>
<td>Gastroesophageal junction</td>
<td>30 (9)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>28 (8)</td>
<td>16 (10)</td>
</tr>
<tr>
<td><strong>Organs with metastases (≥2), n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>246 (75)</td>
<td>119 (73)</td>
</tr>
<tr>
<td><strong>Prior treatment regimens, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>69 (21)</td>
<td>29 (18)</td>
</tr>
<tr>
<td>3</td>
<td>137 (42)</td>
<td>62 (38)</td>
</tr>
<tr>
<td>≥4</td>
<td>124 (38)</td>
<td>72 (44)</td>
</tr>
<tr>
<td><strong>Evaluable for PD-L1 expression, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1% vs &lt;1%</td>
<td>16 (12) vs 114 (88)</td>
<td>10 (16) vs 52 (84)</td>
</tr>
<tr>
<td>≥5% vs &lt;5%</td>
<td>10 (8) vs 120 (92)</td>
<td>7 (11) vs 55 (89)</td>
</tr>
</tbody>
</table>

- Among PD-L1–evaluable patients, baseline characteristics between nivolumab and placebo arms were similar

\(^a\)Includes patients who have either gastric cancer or both gastric and gastroesophageal junction cancer
Efficacy: Survival

**OS**

**Median Overall Survival**
- Nivolumab: 5.32 months
- Placebo: 4.14 months
- Hazard ratio: 0.63 (95% CI, 0.50–0.78)
- p < 0.0001

At risk
- Nivolumab: 330, 275, 19, 10, 5, 3, 0
- Placebo: 163, 121, 4, 3, 3, 1, 0

**PFS**

**Median Progression-Free Survival**
- Nivolumab: 1.61 months
- Placebo: 1.45 months
- Hazard ratio: 0.60 (95% CI, 0.49–0.75)
- p < 0.0001

At risk
- Nivolumab: 330, 131, 83, 46, 31, 19, 8, 4, 2, 0, 0
- Placebo: 163, 41, 17, 9, 7, 4, 2, 2, 1, 1, 0

Japan approved Nivolumab as of Sep. 22th 2017
Best reduction from baseline in tumor burden

### ORR, n (%) 95% CI
- **Nivolumab**
  - Any reduction: 40%
  - ≥30% reduction: 19%
  - ORR: 31 (12)
  - 95% CI: 8–16

- **Placebo**
  - Any reduction: 12%
  - ≥30% reduction: <1%

- Tumor burden reduction was observed regardless of PD-L1 expression level.
Overall survival by PD-L1 expression <1% vs ≥1%

**PD-L1 <1%**

**Median OS, months (95% CI)**

- **Nivolumab (n=114)**: 6.1 (4.8–8.6)
- **Placebo (n=52)**: 4.2 (3.0–6.9)

**Hazard ratio, 0.71**

(95% CI, 0.50–1.01)

**PD-L1 ≥1%**

**Median OS, months (95% CI)**

- **Nivolumab (n=16)**: 5.2 (2.8–9.4)
- **Placebo (n=10)**: 3.8 (0.8–5.0)

No. at Risk

<table>
<thead>
<tr>
<th>Nivolumab</th>
<th>114</th>
<th>10</th>
<th>75</th>
<th>56</th>
<th>49</th>
<th>42</th>
<th>37</th>
<th>24</th>
<th>15</th>
<th>11</th>
<th>7</th>
<th>4</th>
<th>3</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>52</td>
<td>40</td>
<td>27</td>
<td>22</td>
<td>16</td>
<td>14</td>
<td>11</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
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</table>

No. at Risk

<table>
<thead>
<tr>
<th>Nivolumab</th>
<th>16</th>
<th>15</th>
<th>10</th>
<th>7</th>
<th>5</th>
<th>4</th>
<th>4</th>
<th>2</th>
<th>2</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>10</td>
<td>8</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

PD-L1 evaluable patients (N=192)
Patients with Stage IV G/E/GEJa  N = 160  unselected for PDL1 expression, range of prior therapy 0 to >3 (mostly 2-3) sequentially enrolled

- Nivolumab 3 mg/kg IV Q2W  (n = 59)
- Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg IV Q3W for 4 cycles (n = 49)
- Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg IV Q3W for 4 cycles (n = 52)

Checkmate-032: Nivo+Ipi Phase Ib

- All comers
- Exploratory Endpoints: Biomarkers (PD-L1 by Dako, MSI)

Janjigian et al., ASCO 2016, updated ASCO 2017
## Objective Response

<table>
<thead>
<tr>
<th></th>
<th>NIVO 3 n = 59</th>
<th>NIVO 1 + IPI 3 n = 49</th>
<th>NIVO 3 + IPI 1 n = 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)*</td>
<td>7 (12) [5, 23]</td>
<td>12 (24) [13, 39]</td>
<td>4 (8) [2, 19]</td>
</tr>
<tr>
<td>BOR, n (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>6 (10)</td>
<td>11 (22)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>12 (20)</td>
<td>8 (16)</td>
<td>15 (29)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>34 (58)</td>
<td>23 (47)</td>
<td>24 (46)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>6 (10)</td>
<td>6 (12)</td>
<td>9 (17)</td>
</tr>
<tr>
<td>DCR, n (%)†</td>
<td>19 (32)</td>
<td>20 (41)</td>
<td>19 (37)</td>
</tr>
<tr>
<td>Median TTR (range), months</td>
<td>1.6 (1.2 to 4.0)</td>
<td>2.7 (1.2 to 14.5)</td>
<td>2.6 (1.3 to 2.8)</td>
</tr>
<tr>
<td>Median DOR (95% CI), months</td>
<td>7.1 (3.0, 13.2)</td>
<td>7.9 (2.8, NE)</td>
<td>NR (2.5, NE)</td>
</tr>
</tbody>
</table>

BOR, best objective response; DCR, disease control rate; NE, not estimable; NR, not reached.

* Investigator review.
† Patients with a BOR of complete response, partial response, or stable disease.
Best Reduction in Target Lesions

**NIVO 3**
PD-L1–evaluable patients, 38 of 42

**NIVO 1 + IPI 3**
PD-L1–evaluable patients, 38 of 42

**NIVO 3 + IPI 1**
PD-L1–evaluable patients, 34 of 41

* Investigator review.

# Patients with confirmed response (complete or partial response).

† Patients with 0% best reduction in target lesion, including 3 patients with PD-L1 ≥1% (NIVO 3, n = 2; NIVO 3 + IPI 1, n = 1) and 1 patient with PD-L1 <1% (NIVO 1 + IPI 3).

Change truncated to 100%.
Best Reduction in Target Lesions

- Responses were observed regardless of PD-L1 expression

* Investigator review.
# Patients with confirmed response (complete or partial response).
† Patients with 0% best reduction in target lesion, including 3 patients with PD-L1 ≥1% (NIVO 3, n = 2; NIVO 3 + IPI 1, n = 1) and 1 patient with PD-L1 <1% (NIVO 1 + IPI 3).
☐ Change truncated to 100%.
Progression-Free Survival

<table>
<thead>
<tr>
<th>No. at risk:</th>
<th>NIVO 3</th>
<th>NIVO 1 + IPI 3</th>
<th>NIVO 3 + IPI 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>59</td>
<td>49</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

mPFS (95% CI), months
- NIVO 3: 1.4 (1.2, 1.5)
- NIVO 1 + IPI 3: 1.4 (1.2, 3.8)
- NIVO 3 + IPI 1: 1.6 (1.4, 2.6)

6-month PFS rate, %
- NIVO 3: 17
- NIVO 1 + IPI 3: 24
- NIVO 3 + IPI 1: 12

12-month PFS rate, %
- NIVO 3: 8
- NIVO 1 + IPI 3: 17
- NIVO 3 + IPI 1: 10

mPFS, median PFS.
* Investigator review.
Overall Survival

<table>
<thead>
<tr>
<th>Group</th>
<th>mOS (95% CI), months</th>
<th>12-month OS rate, %</th>
<th>18-month OS rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO 3</td>
<td>6.2 (3.4, 12.4)</td>
<td>39</td>
<td>25</td>
</tr>
<tr>
<td>NIVO 1 + IPI 3</td>
<td>6.9 (3.7, 11.5)</td>
<td>35</td>
<td>28</td>
</tr>
<tr>
<td>NIVO 3 + IPI 1</td>
<td>4.8 (3.0, 8.4)</td>
<td>24</td>
<td>13</td>
</tr>
</tbody>
</table>

mOS, median OS.
## Overall Survival by PD-L1 Status

<table>
<thead>
<tr>
<th>OS rate (95% CI), %</th>
<th>NIVO 3</th>
<th>NIVO 1 + IPI 3</th>
<th>NIVO 3 + IPI 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with PD-L1 ≥1%</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>n = 16</td>
<td>n = 10</td>
<td>n = 13</td>
</tr>
<tr>
<td></td>
<td>34 (12, 57)</td>
<td>50 (18, 75)</td>
<td>23 (6, 47)</td>
</tr>
<tr>
<td><strong>Patients with PD-L1 &lt;1%</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>n = 26</td>
<td>n = 32</td>
<td>n = 30</td>
</tr>
<tr>
<td></td>
<td>45 (25, 62)</td>
<td>32 (16, 48)</td>
<td>25 (11, 42)</td>
</tr>
</tbody>
</table>
## Treatment-Related Adverse Events

| Patients, n (%) | NIVO 3  
|----------------|----------------
|                | n = 59         | NIVO 1 + IPI 3  
|                |                | n = 49         | NIVO 3 + IPI 1  
|                |                | n = 52         |                |
| Any TRAE        | 41 (69)        | 41 (84)        | 39 (75)        |
| Serious TRAEs   | 6 (10)         | 21 (43)        | 13 (25)        |
| TRAEs leading to treatment discontinuation | 2 (3)         | 10 (20)        | 7 (13)         |
| TRAEs in ≥15% of patients in any treatment arm | 2 (3)         | 10 (20)        | 5 (10)         |
| ALT increased   | 5 (8)          | 8 (16)         | 5 (10)         |
| AST increased   | 7 (12)         | 8 (16)         | 2 (4)          |
| Decreased appetite | 9 (15)     | 5 (10)         | 3 (6)          |
| Diarrhea        | 9 (15)         | 15 (31)        | 5 (10)         |
| Fatigue         | 20 (34)        | 14 (29)        | 10 (19)        |
| Pruritus         | 10 (17)        | 9 (18)         | 12 (23)        |
| Rash             | 5 (8)          | 10 (20)        | 8 (15)         |

TRAE, treatment-related adverse event.

- One grade 5 TRAE was reported (tumor lysis syndrome in a patient treated with NIVO 3 + IPI 1)
Interim safety & clinical activity in patients with advanced gastric or GE junction adenocarcinoma from a multi-cohort phase 1 study of ramucirumab plus pembrolizumab: JVDF (NCT02443324) Phase 1a/b

**Phase 1a: DLT Assessment (n=6 to 12)**
- **Primary:** Safety and tolerability
- **Secondary:** PK

**Schedule 1: Gastric/GEJ, BTC**
- 3+3 design (n=3 to 6 patients)
- **Ram 8 mg/kg, Day 1 and 8**
- **Pembro 200 mg fixed, Day 1**
- Both IV every 3 weeks

**Phase 1b: Cohort Expansion (n=155)‡**
- **Primary:** Safety and tolerability
- **Secondary:** PK and preliminary efficacy
- **Exploratory:** Biomarkers and immunogenicity

**Cohort A: 15 Gastric/GEJ (2nd-3rd Line)**
- **Cohort A1: 25 BTC (2nd-3rd Line)**
- **Cohort A2: 25 Gastric/GEJ (1st Line)**

**Cohort B: 15 Gastric/GEJ (2nd-3rd Line)**
- **Cohort C: 25 NSCLC (2nd-4th Line)**
- **Cohort D: 25 UC (2nd-4th Line)**
- **Cohort E: 25 NSCLC (1st Line)**

**Interim Analysis**

**Final Analysis**

‡Patients may continue treatment for up to 35 cycles, until confirmed progressive disease or discontinuation for any other reason. DLT dose-limiting toxicity; PK pharmacokinetics; Ram ramucirumab; Pembro pembrolizumab
Figure 2. Tumor Response Over Time in Patients with ≥2nd-Line G/GEJ Adenocarcinoma

Of patients with assessable disease, 57% experienced a decrease in target lesion(s) size.
Figure 3. Tumor Response Over Time in Patients with 1st-Line G/GEJ Adenocarcinoma

Of patients with assessable disease, 77% experienced a decrease in target lesion(s) size.

Figure 5: Progression-free Survival (Interim) in 1st-Line G/GEJ Adenocarcinoma

- **1st-Line Cohort A2**
  - Patients/Events: 28/11
  - Median PFS, mo (95% CI): 5.6 (2.4-NR)
  - 6-mo PFS rate, % (95% CI): 35 (11.5-60.2)

- Median overall survival has not been reached for 1st-Line G/GEJ Adenocarcinoma Cohort A2
## Summary of 2nd/3rd line trials with PD-1/PD-L1 inhibitor

<table>
<thead>
<tr>
<th></th>
<th>Keynote-012</th>
<th>Javelin-lb</th>
<th>Checkmate-032</th>
<th>ATTRACTION-02</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number</td>
<td>39</td>
<td>62</td>
<td>160 (N3 59, N1I3 39, N3I1 52)</td>
<td>330</td>
</tr>
<tr>
<td>2nd line (%)</td>
<td>85%</td>
<td>89%</td>
<td>100/98/100%</td>
<td>29%</td>
</tr>
<tr>
<td>RR</td>
<td>22%</td>
<td>10%</td>
<td>16% (14/26/10%)</td>
<td>11.2%</td>
</tr>
<tr>
<td>DCR</td>
<td>36%</td>
<td>29%</td>
<td>38% (32/43/41%)</td>
<td>40.3%</td>
</tr>
<tr>
<td>PFS (Mo)</td>
<td>1.9</td>
<td>1.5</td>
<td>1.4/1.5/1.6</td>
<td>1.61</td>
</tr>
<tr>
<td>OS (Mo)</td>
<td>≥ 11.4</td>
<td>NA</td>
<td>5/6.9/4.8</td>
<td>5.32</td>
</tr>
<tr>
<td>Asian</td>
<td>50%</td>
<td>40%</td>
<td>2%</td>
<td>100%</td>
</tr>
<tr>
<td>Biomarker enrichment</td>
<td>PD-L1(+)</td>
<td>All comers</td>
<td>All comers</td>
<td>All comers</td>
</tr>
<tr>
<td>PD-L1 (+) ≥1%</td>
<td>40%</td>
<td>50%</td>
<td>21.9%</td>
<td>NA</td>
</tr>
<tr>
<td>ORR in PD-L1(+) ≥1%</td>
<td>22.2%</td>
<td>18.2%</td>
<td>27/44/27</td>
<td>NA</td>
</tr>
<tr>
<td>PD-L1(-)</td>
<td>-</td>
<td>9.1%</td>
<td>12/21/0</td>
<td>NA</td>
</tr>
</tbody>
</table>
Significant prolongation of survival in 2\textsuperscript{nd}/3\textsuperscript{rd} line Tx?

- OS 4.5-9 months with current standard treatment in 2\textsuperscript{nd} line Tx

Bar chart showing survival outcomes for different treatments:
- Tremelimumab
- Pembrolizumab
- Avelumab
- Nivo3
- Nivo1+Ipi3
- Nivo3+Ipi1

Legend:
- PFS
- PPS

PD-L1 +, Phase Ib

Phase III
How to select the proper patients?

• Immunoscore
• PD-L1 IHC
• Immune signature
• TMB
• Neoantigen
• Novel biomarkers??
PD-L1 Expression in Gastric Cancer Samples

- PD-L1 expression was assessed in archival tumor samples using a prototype IHC assay and the 22C3 antibody.
- Positivity was defined as staining in the stroma or in ≥1% of tumor cells.

### Assessing PD-L1 Expression as a Continuous Variable

<table>
<thead>
<tr>
<th></th>
<th>Central Review (N = 35 Evaluable)</th>
<th>Investigator Review (N = 38 Evaluable)</th>
<th>Overall Survival (N = 38 Evaluable)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORR</td>
<td>PFS</td>
<td>ORR</td>
</tr>
<tr>
<td>One-sided P value</td>
<td>0.082</td>
<td>0.269</td>
<td>0.120</td>
</tr>
</tbody>
</table>

Screening: 65 of 162 (40%) patients had PDL1 (+) tumor.
PD-L1 expression by IHC in Bx tissue of metastatic GC

Objectives
I: Feasibility and positive rate of PD-L1 IHC in biopsy tissue
II: Prognostic role and ethnic differences
III: coevaluation of MSI, RNA signature, mutation load

In collaboration with MDACC, MSKCC

- Tumor PD-L1 expression was assessed by a verified Good Manufacturing Practice IHC assay with the 22C3 antibody (PD-L1 IHC 22C3 pharmDx; Agilent Technologies, Carpinteria, CA, USA)
- PD-L1 expression in gastric cancer is determined by combined positive score (CPS), as defined below. Although the result of the calculation can exceed 100, the maximum score is defined as CPS 100%.

\[
CPS = \frac{\text{No. of PD-L1-staining cells (tumor cells, macrophages, lymphocytes)}}{\text{Total No. of viable tumor cells}} \times 100
\]

PD-L1-positive expression if CPS ≥1%
Preliminary data of Korean patients (n=220, 2007-2014)

- PD-L1 positivity was 71.9%
- Not prognostic nor correlation with any clinicopathologic parameters

Figure 3. Histogram of PD-L1 Expression Based on CPS

- Different cut-off?
- Need validation of clinical relevance in conjunction with clinical trials

CPS, combined positive score; PD-L1, programmed death ligand 1.
Incorporation of PD-L1 IHC with histologic molecular subgroup (n=296)

- IHC for PD L1 IHC 22C3 PharmDx assay (Agilent)
- Standard protocol as using a Autostainer link 48 (Dako)
**PD-L1 TPS**

<table>
<thead>
<tr>
<th>Proportion (%)</th>
<th>EBV</th>
<th>MSI</th>
<th>CIN</th>
<th>GS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-49%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 50%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P = 0.009

**OS TPS**

- TPS <1
- TPS ≥1

P = 0.015

5 year OS 72.8% vs 49.7%

**IC PD-L1**

<table>
<thead>
<tr>
<th>Proportion (%)</th>
<th>EBV</th>
<th>MSI</th>
<th>CIN</th>
<th>GS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mild</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>marked</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

P = 0.007

**OS ICPS**

- ICPS (-)
- ICPS (+)

P = 0.035

5 year OS 74.5% vs 66.7%
Case (M/72, after 4th line of Tx)

MK3475 *4 cycles

MK3475 *8 cycles

MK3475 *11 cycles

- TL1 (LN at anterior aspect of pancreas) > 71.6→41.4→35.4→44.9 mm
- TL2 (LN at retropancreatic area) > 53.0→26.8→20.9→21.5 mm
- Target lesion: 124.6→68.2 (-46.7%) →56.3→66.4 mm
- PR at 8 weeks
- PFS 8.8 (9.7 by irRECIST) months
Cases with peritoneal carcinomatosis

- M/35 after 4\textsuperscript{th} line of Tx

- M/72 after 3\textsuperscript{rd} line of Tx

TL1(abdominal wall mass): 26.8→32.6mm (+21.6%), Ascites and pleural effusion increase → PD

PFS 1.6 months

PFS 1.2 months
Different subtype pattern from TCGA

- 92.5%: stage I-III
- 19% Asian (Korea, Vietnam)

TCGA

- EBV + 8.9
- MSI-H 21.7
- CIN 49.8
- GS 19.7

YCC- metastatic GC (n=438)
- EBV + 3.3
- MSI-H 4.8
- CIN 52.2
- GS 39

YCC- operable (TMA 1,302)
- EBV + 6.6
- MSI-H 11.2
- CIN 42
- GS 40.2

Stage dependent biology, Ethnic differences
Triple Negative Gastric Cancer
(EBV negative, MSI negative, HER2 negative)
- Proper screening and new drug development!
Biomarker-driven umbrella trial of Her-2(-) metastatic GC as a 2nd line Tx in combination with paclitaxel

1st line GC

Consent #1

Molecular profiling

Random 1: 4 (N=400)

EGFR positive (2+ or 3+) (N=80)

Power=79.0 %

Apatinib+paclitaxel

PTEN loss (n=50)

Power=70 %

GKS2636771+paclitaxel

Biomarker Group (N=320)

Therapy based on molecular profile

Consent #2

Molecular profiling

IHC screening at Central lab

+ NGS (522genes) with Mutation load

Current status

✓ Start screening at April 2016
✓ 1st patient enrollment at August 2016

-> As of 1st November, 2017
✓ Screening: 204
✓ Enrollment: 82

INCB805428+paclitaxel

TGF-b inhibitor + paclitaxel

Consent #2

Molecular profiling

IHC screening at Central lab

+ NGS (522genes) with Mutation load

INCB805428+paclitaxel
Future directions

Potential for checkpoint inhibitor Ab therapy
± other I-O agents
± antiangiogenics
± cytotoxics
± other targeted therapy

1L
- HER2 negative
  • Pt + FP doublet/triplet based regimen
  • HER2 positive
    cisplatin+5-FU analogue


Maintenance
- 6–8 cycles or until disease progression

2L
- Irinotecan, docetaxel or paclitaxel1
- Ramucirumab ± paclitaxel3,4

3L
- CTx monotherapy
- Nivolumab/ pembrolizumab


If prolonged progression-free interval after 1L, can rechallenge with Pt/FP2

May discontinue due to toxicity or infection

*Not yet approved in EU.