Immunotherapy for advanced gastric cancer

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London & Surrey
Disclosure

- Advisory Board: Eli-Lilly, Bristol Meyers Squibb, MSD, Bayer, Roche, Merck-Serono, Astra-Zeneca
- Research funding: Eli-Lilly, Janssen-Cilag, Sanofi Oncology, Merck-Serono
- Honorarium: Eli-Lilly, Five Prime Therapeutics
History of Checkpoint Inhibitors: Key Milestones

- Checkpoint inhibitors, discovered in the 1990s, have had a major impact on the treatment of multiple tumor types, particularly over the past 7 years.

**APPROVALS BY CANCER TYPE**

- **Melanoma**
- **NSCLC**
- **RCC**
- **Merkel cell carcinoma**
- **dMMR/MSI-H mCRC**

**CANCER TYPES**

- Bladder/urethral cancer
- R/M SCCHN
- Classical Hodgkin lymphoma

**First checkpoint inhibitor (Ipi)**

- 2011
- 2014
- 2015
- 2016
- 2017
- 2018
Immune checkpoint inhibitor mechanism of action

Marrone & Brahmer
Oncology (Williston Park) 2016
# Pembrolizumab in PD-L1 positive gastric cancer KEYNOTE-012

<table>
<thead>
<tr>
<th></th>
<th>Central review</th>
<th>Investigator Review</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>36</td>
<td>39</td>
</tr>
<tr>
<td><strong>ORR</strong> (95% CI)</td>
<td>22% (10%-39%)</td>
<td>33% (19%-50%)</td>
</tr>
<tr>
<td>Median duration of response</td>
<td>40 weeks</td>
<td></td>
</tr>
<tr>
<td>Median PFS</td>
<td>1.9 months</td>
<td></td>
</tr>
<tr>
<td>Six-month PFS</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>11.4 months</td>
<td></td>
</tr>
<tr>
<td>Six-month OS</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>12-month OS</td>
<td>42%</td>
<td></td>
</tr>
</tbody>
</table>

40% of screened population were PD-L1 positive  
Muro et al Lancet Oncol 2016
KEYNOTE-059: multicohort pembrolizumab study in gastric/OGJ adenocarcinoma

Cohort 1
• ≥2 prior lines of CT
  n=259

Pembrolizumab
200 mg q3w

For 24 months or until progression, intolerable toxicity, or other reason

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

Cohort 2
• No prior therapy
  n=25

Pembrolizumab 200 mg q3w +
Cisplatin 80 mg/m² q3w +
5-FU 800 mg/m² q3w or
Capecitabine 1000 mg/m² q3w *

Primary Endpoints: ORR by RECIST v1.1, safety and tolerability
Secondary Endpoint: DOR by central review, PFS, OS
Exploratory Biomarker Endpoints: Efficacy by microsatellite instability and gene expression profile

Cohort 3
• No prior therapy
• PD-L1 positive
  n=31

Pembrolizumab
200 mg q3w

1 Fuchs C, et al. JAMA Oncol 2018; 2 Bang et al. ASCO 2017; 3 Catenacci et al. WCGIC 2017
KEYNOTE-059: single arm pembrolizumab as third or subsequent line treatment for advanced gastric and OGJ adenocarcinoma

<table>
<thead>
<tr>
<th></th>
<th>ITT</th>
<th>PD-L1+ve</th>
<th>PD-L1-ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>259</td>
<td>148 (57.1%)</td>
<td>109 (42.1%)</td>
</tr>
<tr>
<td>ORR</td>
<td>11.6%</td>
<td>15.5%</td>
<td>6.4%</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(8.0%-16.1%)</td>
<td>(10.1%-22.4%)</td>
<td>(2.6%-12.8%)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>2.0 months</td>
<td>2.1 months</td>
<td>2.0 months</td>
</tr>
<tr>
<td>Six-month PFS</td>
<td>14.1%</td>
<td>HR: 0.68 (95% CI: 0.52-0.88)</td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>5.6 months</td>
<td>5.8 months</td>
<td>4.6 months</td>
</tr>
<tr>
<td>Six-month OS</td>
<td>46.5%</td>
<td>PD-L1+ve vs. -ve</td>
<td></td>
</tr>
<tr>
<td>12-month OS</td>
<td>23.4%</td>
<td>HR: 0.76 (95% CI: 0.57-1.00)</td>
<td></td>
</tr>
</tbody>
</table>

Fuchs et al JAMA Oncol 2018; Kulangara et al Arch Pathol Lab Med 2018
KEYNOTE-059: single arm pembrolizumab survival by PD-L1 status (CPS ≥1)

Overall survival

Progression free survival

Kulangara et al Arch Pathol Lab Med 2018
Randomised third and subsequent line placebo-controlled phase III nivolumab study in gastric and GEJ adenocarcinoma (ONO 12/ATTRACTION-2)

- Advanced gastric or GEJ adenocarcinoma
- Disease progression on 2 lines of systemic therapy

Stratification:
1) Country (Japan vs Korea vs Taiwan)
2) ECOG PS (0 vs 1)
3) Number of organs with metastases (< 2 vs ≥ 2)

R

Nivolumab 3mg/kg iv every 2 weeks

2:1 n=330

Placebo every 2 weeks

n=163

Primary endpoint: Overall survival

Kang et al Lancet 2017
Overall Survival

Kang et al Lancet 2017
**Survival (2-year follow up)**

**Overall survival**

- The 2-year survival rate was higher with nivolumab (10.6%) vs placebo (3.2%)

**Progression free survival**

- The 2-year PFS rate was 3.8% with nivolumab, whereas all patients had disease progression with placebo

Satoh et al ESMO 2018
CHECKMATE CA209-032 trial design

N=160

Key Eligibility Criteria
- Locally advanced or metastatic gastric, oesophageal, or GOJ cancer
- Prior progression on ≥1 prior chemotherapy
- ECOG performance status 0 or 1

n=59
Nivolumab 3 mg/kg Q2W

n=49
Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg Q3W for 4 cycles*

n=52
Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg Q3W for 4 cycles*

- **Primary Endpoint:** ORR by RECIST v1.1
- **Secondary and Exploratory Endpoints:** TRAEs, OS, PFS, DOR, PK/PD/Immunogenicity, PD-L1, MSI
- **79% of patients had received ≥2 prior therapy lines**

* Followed by single-agent nivolumab 3 mg/kg IV Q2W.

Janjigian et al J Clin Oncol 2018
Mirroring CHECKMATE-032 with ATTRACTON 2 patient population

# ATTRACTON-2 Phase 3 Study (Asian)
- Unresectable advanced or recurrent G/GEJ cancer
- Refractory to/intolerant of ≥ 2 standard therapy regimens

- Randomization
- Nivolumab 3 mg/kg IV Q2W (n = 330)
- Placebo (n = 163)

# CheckMate-032 Phase 1/2 Study (Western)
- Patients with advanced/metastatic G/GEJ/E cancer with progression on ≥ 1 prior chemotherapy (N = 160)
- G/GEJ/E cancer nivolumab monotherapy 3 mg/kg IV Q2W cohort (n = 59)
- Subset of patients with G/GEJ cancer and ≥ 2 prior regimens (n = 42)

*Data cutoff for ATTRACTON-2 was August 2016; †Data cutoff for CheckMate-032 was March 2016, except for OS analyses (November 2016)

DOR = duration of response; E = esophageal; G = gastric; GEJ = gastroesophageal junction

Chau et al GI ASCO 2018; Ott et al GI ESMO 2017
Patient enrolment in ATTRACTION-2 and CHECKMATE-032

Chau et al ASCO GI 2018
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>ATTRACTION-211</th>
<th>CheckMate-032 G/GEJ cancer12,b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo n = 163</td>
<td>Nivolumab n = 330</td>
</tr>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>61 (26–83)</td>
<td>62 (20–83)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>119 (73)</td>
<td>229 (69)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>163 (100)</td>
<td>329 (&gt;99)</td>
</tr>
<tr>
<td>White</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Black</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Otherc</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>48 (29)</td>
<td>95 (29)</td>
</tr>
<tr>
<td>1</td>
<td>115 (71)</td>
<td>235 (71)</td>
</tr>
<tr>
<td><strong>Primary site of disease, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric</td>
<td>135 (83)</td>
<td>272 (82)</td>
</tr>
<tr>
<td>Gastroesophageal junction</td>
<td>12 (7)</td>
<td>30 (9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>16 (10)</td>
<td>28 (8)</td>
</tr>
<tr>
<td><strong>Prior lines of treatment, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>29 (18)</td>
<td>69 (21)</td>
</tr>
<tr>
<td>3</td>
<td>62 (38)</td>
<td>137 (42)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>72 (44)</td>
<td>124 (38)</td>
</tr>
</tbody>
</table>

*Classified as Native Hawaiian or other Pacific Islander; Patients with ≥ 2 prior regimens

Chau et al ASCO GI 2018
Clinical efficacy in Asian and Western populations

<table>
<thead>
<tr>
<th></th>
<th>ATTRACTION-2</th>
<th>CheckMate-032 G/GEJ cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo n = 163</td>
<td>Nivolumab n = 330</td>
</tr>
<tr>
<td>Median OS (95% CI), mo</td>
<td>4.1 (3.4, 4.9)</td>
<td>5.3 (4.6, 6.4)</td>
</tr>
<tr>
<td></td>
<td><em>P</em> &lt; 0.0001 HR: 0.63 (0.51, 0.78)</td>
<td>NA</td>
</tr>
<tr>
<td>12-mo OS rate (95% CI), %</td>
<td>11 (6, 17)</td>
<td>26 (21, 32)</td>
</tr>
<tr>
<td>Median PFS (95% CI), mo</td>
<td>1.45 (1.45, 1.5)</td>
<td>1.6 (1.5, 2.3)</td>
</tr>
<tr>
<td></td>
<td><em>P</em> &lt; 0.0001 HR: 0.60 (0.49, 0.75)</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Nivolumab data shown are from different clinical trials and should not be directly compared; median follow-up (in surviving patients) was 8.9 months (IQR: 6.6–12.4) in the nivolumab group and 8.6 months (IQR: 5.65–11.4) in the placebo group in ATTRACTION-2; median follow-up (from first dose to data cutoff) was 27.9 months (range: 17.0–35.2) for OS and 19.75 months (range: 9.5–27.7) for PFS in CheckMate-032; *Patients with ≥2 prior regimens IQR = interquartile range

- ORR (by investigator assessment) with nivolumab was 11% (95% CI: 8, 16) in Asian patients and 17% (95% CI: 7, 31) in Western patients

Chau et al ASCO GI 2018
Randomised third line phase III avelumab study in gastric and GEJ adenocarcinoma (JAVELIN 300)

Advanced gastric or GEJ adenocarcinoma
Disease progression on two lines of prior therapy
PD-L1 +ve or -ve

Paclitaxel or irinotecan
Avelumab

Primary endpoint: Overall survival

Bang et al Ann Oncol 2018
Randomised third line phase III avelumab study in gastric and GEJ adenocarcinoma (JAVELIN 300)

**Overall survival**

<table>
<thead>
<tr>
<th>Arm</th>
<th>Median OS, months (95% CI)</th>
<th>6-month OS rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avelumab</td>
<td>4.6 (3.6–5.7)</td>
<td>41.0% (33.7–46.1)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>5.0 (4.6–5.3)</td>
<td>45.0% (37.6–52.1)</td>
</tr>
</tbody>
</table>

**Progression free survival**

<table>
<thead>
<tr>
<th>Arm</th>
<th>Median PFS, months (95% CI)</th>
<th>3-month PFS rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avelumab</td>
<td>1.4 (1.4–1.5)</td>
<td>15.1% (13.8–16.5)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>2.7 (1.8–2.8)</td>
<td>39.2% (31.3–46.9)</td>
</tr>
</tbody>
</table>

Bang et al Ann Oncol 2018
Randomised third line phase III avelumab study in gastric and GEJ adenocarcinoma (JAVELIN 300)

Bang et al Ann Oncol 2018
Randomised second line phase III pembrolizumab study in gastric and GEJ adenocarcinoma (KEYNOTE-061)

Advanced gastric or GEJ adenocarcinoma
Disease progression on first line FP + platinum treatment

Paclitaxel 80mg/m² on Days 1, 8 and 15 every 4 weeks
Pembrolizumab 200mg Day 1 every 3 weeks

n=592

Stratification:
1) Geographic region
2) Time to Progression on 1st line therapy
3) PD-L1 expression status

Primary endpoint: PD-L1 Combined Positive Score (CPS) ≥1; Progression free and Overall survival

Shitara et al Lancet 2018
Randomised second line phase III pembrolizumab study in gastric and GEJ adenocarcinoma (KEYNOTE-061)

PD-L1 CPS ≥1
Advanced gastric or GEJ adenocarcinoma
Disease progression on first line FP + platinum treatment

n=199
Paclitaxel 80mg/m² on Days 1, 8 and 15 every 4 weeks

n=196
Pembrolizumab 200mg Day 1 every 3 weeks

Primary endpoint: PD-L1 CPS ≥1 PFS and OS

Shitara et al Lancet 2018
Randomised second line phase III pembrolizumab study in gastric and GEJ adenocarcinoma (KEYNOTE-061)

Overall survival

A

<table>
<thead>
<tr>
<th>PAC</th>
<th>PEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS (months)</td>
<td>8.3</td>
</tr>
<tr>
<td>12-m OS</td>
<td>27%</td>
</tr>
<tr>
<td>18-m OS</td>
<td>15%</td>
</tr>
</tbody>
</table>

Post-hoc weighted log-rank test 1-sided p=0.0009

Progression free survival

<table>
<thead>
<tr>
<th>PAC</th>
<th>PEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS (months)</td>
<td>4.1</td>
</tr>
<tr>
<td>12-m OS</td>
<td>9%</td>
</tr>
</tbody>
</table>

ORR

<table>
<thead>
<tr>
<th>PAC</th>
<th>PEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>14%</td>
<td>16%</td>
</tr>
</tbody>
</table>
KEYNOTE-061: subgroup survival

Overall survival for CPS ≥10

OS for CPS ≤1

PFS for CPS ≤1

Shitara et al Lancet 2018
Randomised first line phase III pembrolizumab study in gastric and GEJ adenocarcinoma (KEYNOTE-062)

Previously untreated advanced PD-L1 +ve gastric or GEJ adenocarcinoma

n=750

Placebo + Cisplatin/FP

Pembrolizumab + Cisplatin/FP

Pembrolizumab alone

Primary endpoint: PD-L1 CPS ≥1 PFS and OS

Co- endpoint: PD-L1 CPS ≥10 PFS and OS

NCT02494583
Randomised first line phase III pembrolizumab study in gastric and GEJ adenocarcinoma (CHECKMATE-649)

Previously untreated advanced gastric or GEJ adenocarcinoma PD-L1 +ve or -ve

n=1,266

FOLFOX or CAPOX

Nivolumab + FOLFOX or CAPOX

Nivolumab + ipilimumab

Primary endpoint: Overall survival in patients with PD-L1+ tumors (PD-L1 ≥ 1% expression; Dako 28-8 pharmDx assay)

NCT02872116
Randomised phase III avelumab study in gastric and GEJ adenocarcinoma as maintenance treatment after first line therapy (JAVELIN 100)

Previously untreated patients with unresectable, locally advanced or metastatic HER2-GC/GEJC unselected for PD-L1 expression

Induction phase (12 weeks)
- Oxaliplatin + 5-fluorouracil (FOLFOX) or capecitabine (CAPOX)

Maintenance phase
- Continuation of 1L chemotherapy or BSC alone
- Avelumab 10 mg/kg Q2W
  Treatment until confirmed disease progression, unacceptable toxicity, or withdrawal

Primary endpoint: OS
Primary objective:
To assess the efficacy of avelumab compared with chemotherapy in terms of OS in all randomized patients or in PD-L1+ patients

Secondary endpoints:
PFS, BOR, safety, PROs/QOL

NCT02625610
Moehler et al Future Oncol 2018
PLATFORM Trial (1\textsuperscript{st} line maintenance)
1\textsuperscript{st} line metastatic / LA OG adenocarcinoma

Her-2 Negative
- Chemo x6-8
- Surveillance
- Durvalumab Maintenance
- Capecitabine Maintenance
- RAM + capecitabine Maintenance
- Re-biopsy
- Exploratory Biomarker Evaluation (Tissue and Serial Blood Tests)

Her-2 Positive
- Chemo x6 + trastuzumab
- Trial Entry
- >SD on CT
- >SD on CT
- RAM + capecitabine Maintenance
- Trastuzumab Maintenance
- Tras. + durvalumab Maintenance
- 1:1

Registration

1\textsuperscript{st} Endpoint: PFS, 2\textsuperscript{nd} Endpoint: RR, OS, Toxicity

735 pts registered
233 randomised
Multimodality treatment of OGJ/ gastric adenocarcinoma

Pre-operative
- Pre-operative chemoradiation
  - Surgery

Pre-operative chemotherapy
  - Surgery

Pre-operative chemotherapy
  - Surgery
  - Post-operative chemotherapy

Post-operative chemotherapy

Surgery

Post-operative}

Surgery

Post-operative

Chemoradiation
Peri-operative immunotherapy

Pre-operative

Pre-operative chemoradiation

Surgery

Post-operative nivolumab

Post-operative

CHECKMATE 577

n=760

Screening

• Age ≥18 years
• Stage II/III carcinoma of the E/GEJ
• Completed pre-operative CRT followed by surgery
• Residual pathologic disease following complete resection

Treatment

Randomized

Nivolumab

Placebo

Post-treatment follow-up
Peri-operative immunotherapy

Pre-operative

Pre-operative Chemo + PEMBRO

Surgery

Patients with resectable adenocarcinoma of OGI and stomach

Post-operative Chemo + PEMBRO

KEYNOTE 585

CX x3/ (FLOT ×4)

n=∼800

CX x3
(FLOT ×4)

Surgery

CX x3
(FLOT ×4)

Surgery

Pembro q3w × ~1 year

Post-operative

CX x3
(FLOT ×4)

Surgery

CX x3
(FLOT ×4)

pembrolizumab

CX x3
(FLOT ×4)

pembrolizumab
## ICONIC STUDY DESIGN

<table>
<thead>
<tr>
<th>STEPS</th>
<th>SCREENING</th>
<th>PRE-OP FLOT-A</th>
<th>SURGERY</th>
<th>POST-OP FLOT-A</th>
<th>FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRIAL TREATMENT</td>
<td>Operable stomach or oesophageal cancer</td>
<td>4 x FLOT + Avelumab</td>
<td>CT and PET scan, staging laparoscopy</td>
<td>4 x FLOT + Avelumab</td>
<td>Follow-up for 5 years or until recurrence</td>
</tr>
<tr>
<td>INVESTIGATIONS</td>
<td>--</td>
<td>CT scan and surgical fitness assessment</td>
<td>--</td>
<td>--</td>
<td>Blood for tumour markers</td>
</tr>
<tr>
<td>TRANSLATION</td>
<td>Liquid Biopsy</td>
<td>Endoscopic Biopsy</td>
<td>Faecal Microbiome</td>
<td>Recurrence Biopsy</td>
<td>Mansukhani et al ASCO 2018</td>
</tr>
</tbody>
</table>
Peri-operative immunotherapy: ICONIC

Sponsor: Royal Marsden Hospital
PI: Marco Gerlinger
N=40-46
Primary endpoint: pCR rate

Mansukhani et al ASCO 2018
Combined PD-1 and CTLA-4 blockade

Quail & Joyce Nature Med 2013
CHECKMATE CA209-032

trial design

N=160

Key Eligibility Criteria

- Locally advanced or metastatic gastric, oesophageal, or GOJ cancer
- Prior progression on ≥1 prior chemotherapy
- ECOG performance

n=59

Nivolumab 3 mg/kg Q2W

n=49

Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg Q3W for 4 cycles*

n=52

Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg Q3W for 4 cycles*

- **Primary Endpoint**: ORR by RECIST v1.1
- **Secondary and Exploratory Endpoints**: TRAEs, OS, PFS, DOR, PK/PD/Immunogenicity, PD-L1, MSI
- 79% of patients had received ≥2 prior therapy lines

Janjigian et al J Clin Oncol 2018

* Followed by single-agent nivolumab 3 mg/kg IV Q2W.
# Nivolumab ± Ipilimumumab: CheckMate 032

Janjigian et al J Clin Oncol 2018

<table>
<thead>
<tr>
<th>Response Category (RECIST 1.1)</th>
<th>Nivo 3 mg/kg (n=59)</th>
<th>Nivo 1 mg/kg + Ipi 3 mg/kg (n=49)</th>
<th>Nivo 3 mg/kg + Ipi 1 mg/kg (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate, %</td>
<td>12</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td>Complete response, %</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Partial response, %</td>
<td>10</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Stable disease, %</td>
<td>20</td>
<td>16</td>
<td>29</td>
</tr>
<tr>
<td>Progressive disease, %</td>
<td>58</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td>Not determined, %</td>
<td>10</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>Disease control rate, %</td>
<td>32</td>
<td>41</td>
<td>37</td>
</tr>
<tr>
<td>Median time to response (range), months</td>
<td>1.6 (1.2–4.0)</td>
<td>2.7 (1.2–14.5)</td>
<td>2.6 (1.3–2.8)</td>
</tr>
<tr>
<td>Median duration of response (95% CI), months</td>
<td>7.1 (3.0, 13.2)</td>
<td>7.9 (2.8, NE)</td>
<td>NR (NE, NE)</td>
</tr>
</tbody>
</table>
Overall Survival and Progression-Free Survival

### Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>N3  (n=59)</th>
<th>N1 + I3 (n=49)</th>
<th>N3 + I1 (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OS Rates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mo</td>
<td>39%</td>
<td>35%</td>
<td>24%</td>
</tr>
<tr>
<td>18 mo</td>
<td>25%</td>
<td>28%</td>
<td>13%</td>
</tr>
<tr>
<td>Median</td>
<td>6.2 (3.4, 12.4)</td>
<td>6.9 (3.7, 11.5)</td>
<td>4.8 (3.0, 8.4)</td>
</tr>
</tbody>
</table>

### Progression-Free Survival

<table>
<thead>
<tr>
<th></th>
<th>N3  (n=59)</th>
<th>N1 + I3 (n=49)</th>
<th>N3 + I1 (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS Rates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td>17%</td>
<td>24%</td>
<td>12%</td>
</tr>
<tr>
<td>12 mo</td>
<td>8%</td>
<td>17%</td>
<td>10%</td>
</tr>
<tr>
<td>Median</td>
<td>1.4 (1.2, 1.5)</td>
<td>1.4 (1.2, 3.8)</td>
<td>1.6 (1.4, 2.6)</td>
</tr>
</tbody>
</table>

Janjigian et al J Clin Oncol 2018
Randomised first line phase III pembrolizumab study in gastric and GEJ adenocarcinoma (CHECKMATE-649)

Previously untreated advanced gastric or GEJ adenocarcinoma PD-L1 +ve or -ve

n=1,266

FOLFOX or CAPOX

Nivolumab + FOLFOX or CAPOX

Nivolumab + ipilimumab

Primary endpoint: Overall survival in patients with PD-L1+ tumors (PD-L1 ≥ 1% expression; Dako 28-8 pharmDx assay)

NCT02872116
Tumour microenvironment

Combined IO-IO strategy

Quail & Joyce Nature Med 2013
FRACTION-Gastric Cancer
A Phase 2, Fast Real-time Assessment of Combination Therapies in Immuno-ONcology Study in Participants With Advanced Gastric Cancer

- Patients entering the study would be enrolled/randomized across all open combinations according to “track” they are on in a 1:1:1… basis
- New combination partners added over time via “Sub-Protocols” as safety data at the dose/schedule of the combination become available
- External Safety Monitoring Board (SMB) to assess safety

Combo 1: nivo + ipi
Combo 2: nivo + relatlimab
Combo 3: nivo + IDO inhibitor

NCT02935634
THE ROYAL MARSDEN

MORPHEUS Gastric

Screening → Stage 1 → Stage 2

Indication

Entry Biopsy (Stage 1)

CIT Combinations: Experimental Arm(s)

Control

PD / Re-Entry Biopsy (Stage 2)

CIT Combinations: Experimental Arm(s)

Mandatory Serial Biopsy Arms*

R

1L Cohort | 2L Cohort
---|---
mFOLFOX-6 | Ramucirumab + paclitaxel
Atezolizumab + cabimetinib + mFOLFOX-6 | Atezolizumab + cabimetinib
Atezolizumab + mFOLFOX-6 | Atezolizumab + PEGPH20
— | Atezolizumab + BL-8040
— | Atezolizumab + linagliptin

CIT, cancer immunotherapy; PD, progressive disease; R, randomisation.

*The sponsor may open enrolment in separate mandatory serial biopsy arms to enable patients who are willing to undergo serial biopsies to receive treatment with an experimental combination that has demonstrated clinical activity during the preliminary phase.

Chau et al ESMO 2018
**Tumour microenvironment**

**Tumor vasculature**
- Bevacizumab (anti-VEGF-A)
- S-265610 (anti-CXCR2)
- Sunitinib (RTK inhibitor)
- VEGF-Trap (decoy receptor)

**Immune activation**
- Iplimumab (anti-CTLA-4)
- Nivolumab (anti-PD1R)
- Lambroluzumab (anti-PD-L1)

**Repolarization and re-education**
- BLZ945 (anti-CSF-1R)
- CD40 mAb

**Metastasis and/or outgrowth**
- MLN1202 (anti-CCR2)

**Altered immune cell recruitment, expansion and depletion**
- PLX3397 (anti-CSF-1R and anti-KIT)
- AMD3100 (anti-CXCR4)
- S-265610 (anti-CXCR2)
- GW2580 (anti-CSF-1R)
- Trabectedin (chemotherapy)

*Quail & Joyce Nature Med 2013*
Tumour infiltrating immune cells have different pro-tumour pro-angiogenic roles

Myeloid-derived - M-MDSC: monocyte-myeloid derived suppressor cells
PMN: polymorphonuclear
TAM: tumour associated macrophages
M2: polarised phenotype
Lymphoid-derived - Treg: T regulatory cells
ILC: innate lymphoid cells

Mortara et al Curr Opin Pharmacol 2017
Scientific rationale for combining anti-angiogenics and checkpoint inhibition

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/APCs)
3. Priming and activation (APCs and T cells)
4. Trafficking of T cells to tumours (CTLs)
5. Infiltration of T cells into tumours (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (immune and cancer cells)

Promotion of T-cell priming and activation via dendritic cell maturation

Normalisation of the tumour vasculature for increased T-cell tumour infiltration

Establishing an immune-permissive tumour microenvironment by decreasing MDSC and Treg populations

Figure adapted from Chen DS, Mellman I.

IMpower150 study design

Stage IV or recurrent metastatic non-squamous NSCLC
Chemotherapy-naive
Tumour tissue available for biomarker testing
Any PD-L1 IHC status

Stratification factors:
• Sex
• PD-L1 IHC expression
• Liver metastases

N = 1202

The principal question is to assess whether the addition of atezolizumab to Arm C provides clinical benefit

Arm A
Atezolizumab\(^b\) + Carboplatin\(^c\) + Paclitaxel\(^d\)
4 or 6 cycles

Arm B
Atezolizumab\(^b\) + Carboplatin\(^c\) + Paclitaxel\(^d\)
+ Bevacizumab\(^e\)
4 or 6 cycles

Arm C (control)
Carboplatin\(^c\) + Paclitaxel\(^d\)
+ Bevacizumab\(^e\)
4 or 6 cycles

Treated with atezolizumab until PD by RECIST v1.1 or loss of clinical benefit
AND/OR
Treated with bevacizumab until PD by RECIST v1.1

Survival follow-up

Maintenance therapy
(no crossover permitted)

1:1:1

R

Socinski et al N Engl J Med 2018

Note:
\(^a\) Patients with a sensitising EGFR mutation or ALK translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies. \(^b\) Atezolizumab: 1200 mg IV q3w. \(^c\) Carboplatin: AUC 6 IV q3w.
\(^d\) Paclitaxel: 200 mg/m\(^2\) IV q3w. \(^e\) Bevacizumab: 15 mg/kg IV q3w.
IMpower 150 survival endpoints

Socinski et al N Engl J Med 2018
JVDF Ramucirumab + pembrolizumab
Phase 1a/b Study Design

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

Schedule 2: Gastric/GEJ, NSCLC, UC
3+3 design (n= 3 to 6 patients)
Ram 10 mg/kg, Day 1
Pembro 200 mg fixed, Day 1
Both IV every 3 weeks

Phase 1b: Cohort Expansion (n=155)a
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)

Final Analysis

Interim Analysis
Primary:
Safety and tolerability
Secondary:
PK

aPatients 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

Herbst, Chau et al ASCO 2018
## Tumor Response by PD-L1 in Evaluable Patients

<table>
<thead>
<tr>
<th>PD-L1 Status</th>
<th>G/GEJ (2nd-3rd line)</th>
<th></th>
<th>NSCLC (2nd-4th line)</th>
<th></th>
<th>UC (2nd-4th line)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CPS &lt;1%</td>
<td>CPS ≥1%</td>
<td>TPS &lt;1%</td>
<td>TPS ≥1%</td>
<td>CPS &lt;1%</td>
<td>CPS ≥1%</td>
</tr>
<tr>
<td></td>
<td>n=17</td>
<td>n=22</td>
<td>n=11</td>
<td>n=11</td>
<td>n=11</td>
<td>n=12</td>
</tr>
<tr>
<td><strong>ORR, % (95% CI)</strong></td>
<td>6 (0.1-28.7)</td>
<td>9 (1.1-29.2)</td>
<td>18 (2.3-51.8)</td>
<td>45 (16.7-76.6)</td>
<td>0</td>
<td>25 (5.5-57.2)</td>
</tr>
<tr>
<td>Time to response</td>
<td>1.4</td>
<td>2.8 (1.4-4.1)</td>
<td>2.8 (2.8-2.8)</td>
<td>1.4 (1.3-5.3)</td>
<td>-</td>
<td>2.8 (1.3-5.5)</td>
</tr>
<tr>
<td>Duration of response</td>
<td>4.4</td>
<td>12.1 (6.7-17.5)</td>
<td>11.1 (11.1-NR)</td>
<td>NR (NR-NR)</td>
<td>-</td>
<td>8.3 (4.6-16.8)</td>
</tr>
<tr>
<td><strong>Disease control, % (95% CI)</strong></td>
<td>41 (18.4-67.1)</td>
<td>64 (40.7-82.8)</td>
<td>82 (48.2-97.7)</td>
<td>91 (58.7-99.8)</td>
<td>27 (6-61)</td>
<td>67 (34.9-90.1)</td>
</tr>
<tr>
<td>Duration of stable disease</td>
<td>4.1 (1.7-9.2)</td>
<td>6.9 (2.6-14.0)</td>
<td>8.3 (2.7-13.6)</td>
<td>4.0 (2.8-6.9)</td>
<td>2.8 (1.9-13.1)</td>
<td>2.6 (2.1-3.7)</td>
</tr>
</tbody>
</table>

Data are median, months (%) unless otherwise specified

ORR= objective response rate; CPS= combined positive score; TPS= tumor proportion score; NR= not reached
### Efficacy by PD-L1 in G/GEJ
(2nd-3rd Line)

#### Progression free survival

<table>
<thead>
<tr>
<th>PD-L1</th>
<th>No./Events</th>
<th>Median PFS, Mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>17/17</td>
<td>1.7 (1.3-4.0)</td>
</tr>
<tr>
<td>Positive</td>
<td>22/19</td>
<td>4.6 (2.3-8.5)</td>
</tr>
</tbody>
</table>

#### Overall survival

<table>
<thead>
<tr>
<th>PD-L1</th>
<th>No./Events</th>
<th>Median OS, Mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>17/16</td>
<td>5.2 (1.3-8.6)</td>
</tr>
<tr>
<td>Positive</td>
<td>22/15</td>
<td>12.6 (4.7-20.3)</td>
</tr>
</tbody>
</table>

Herbst, Chau et al ASCO 2018
JVDF Ramucirumab + pembrolizumab
Phase 1a/b Study Design

Phase 1a: DLT Assessment (n=6 to 12)

- **Primary**: Safety and tolerability
- **Secondary**: PK

<table>
<thead>
<tr>
<th>Schedule 1: Gastric/GEJ, BTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>3+3 design (n= 3 to 6 patients)</td>
</tr>
<tr>
<td><strong>Ram 8 mg/kg, Day 1 and 8</strong></td>
</tr>
<tr>
<td>Pembro 200 mg fixed, Day 1</td>
</tr>
<tr>
<td>Both IV every 3 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Schedule 2: Gastric/GEJ, NSCLC, UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>3+3 design (n= 3 to 6 patients)</td>
</tr>
<tr>
<td><strong>Ram 10 mg/kg, Day 1</strong></td>
</tr>
<tr>
<td>Pembro 200 mg fixed, Day 1</td>
</tr>
<tr>
<td>Both IV every 3 weeks</td>
</tr>
</tbody>
</table>

Phase 1b: Cohort Expansion (n=155)\(^a\)

- **Primary**: Safety and tolerability
- **Secondary**: PK and preliminary efficacy
- **Exploratory**: Biomarkers and immunogenicity

<table>
<thead>
<tr>
<th>Cohort A: 15 Gastric/GEJ (2nd-3rd Line)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort A1: 25 BTC (2nd-3rd Line)</td>
</tr>
<tr>
<td><strong>Cohort A2: 25 Gastric/GEJ (1st Line)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cohort B: 15 Gastric/GEJ (2nd-3rd Line)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort C: 25 NSCLC (2nd-4th Line)</td>
</tr>
<tr>
<td>Cohort D: 25 UC (2nd-4th Line)</td>
</tr>
<tr>
<td><strong>Cohort E: 25 NSCLC (1st Line)</strong></td>
</tr>
</tbody>
</table>

*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
## ORR in Evaluable Patients (PD-L1 all comers)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1st-Line Cohort A2</th>
</tr>
</thead>
<tbody>
<tr>
<td>All treated patients</td>
<td>n=28</td>
</tr>
<tr>
<td>Median follow-up duration, mo (95% CI)</td>
<td>8.1 (5.7-9.9)</td>
</tr>
<tr>
<td>Best overall response, n (%)</td>
<td></td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>-</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>7 (25)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>12 (43)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Not Evaluable</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Objective response rate</td>
<td>25%</td>
</tr>
<tr>
<td>Disease control ratea</td>
<td>68%</td>
</tr>
<tr>
<td>Median duration of response, mo (95%CI)</td>
<td>10 (9.7-10.3)b</td>
</tr>
<tr>
<td>Median time to response, mo (95% CI)</td>
<td>2.7 (1.3-2.8)</td>
</tr>
<tr>
<td>Duration of stable disease, mo (95% CI)</td>
<td>5.4 (3.2-8.6)</td>
</tr>
</tbody>
</table>

*a* patients with best response of CR, PR, or SD.

*b* As of the data cutoff, 5 (71%) of 7 patients with a confirmed response were still on treatment.

NR= not reached

Chau et al GI ASCO 2018
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.

* Confirmed PR

Chau et al GI ASCO 2018
How to select optimal patients?
Biomarkers for PD-1/PD-L1 antibodies

• IHC – which one? Which cut-off? 1%, 5%, 10%, 50%; Tumour cells or immune cells?
• Microsatellite instability
• EBV status
• T-cell inflamed gene expression profiling score
• Total Mutational burden (TMB)
Biomarkers for PD-1/PD-L1 antibodies

- IHC – which one? Which cut-off? 1%, 5%, 10%, 50%; Tumour cells or immune cells?
- Microsatellite instability
- EBV status
- T-cell inflamed gene expression profiling score
- Total Mutational burden (TMB)
PD-L1 expression in patients with metastatic gastric cancer

\[
\text{CPS} = \frac{\text{No. PD-L1-stained cells}}{\text{Total No. of viable tumor cells}} \times 100
\]

Kulangara et al. Arch Pathol Lab Med 2018

PD-L1 negative

PD-L1 positive based on Combined Positive Score (CPS) ≥1.
PD-L1 expression (CPS) in patients with metastatic gastric cancer

- 72% of patients (n=220) were PD-L1 positive assessed by the DAKO 22C3 IHC kit
- Neither prognostic nor correlated with clinico-pathological parameters

Kim et al ASCO 2017

PD-1, programmed death receptor-1; PD-L1, programmed death ligand 1
PD-L1 positive based on Combined Positive Score (CPS) ≥1%.
**ATTRACTION 2 survival by PD-L1 status (TPS)**

- Among the 192 patients with samples that could be assessed (DAKO 28-8 pharmDx assay), 16 (12.3%) of 130 patients in the nivolumab group and ten (16.1%) of 62 patients in the placebo group had PD-L1-positive tumours.

Kang et al Lancet 2017
**KEYNOTE-059: single arm pembrolizumab as third or subsequent line treatment for advanced gastric and OGJ adenocarcinoma**

<table>
<thead>
<tr>
<th></th>
<th>ITT</th>
<th>PD-L1+ve</th>
<th>PD-L1-ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>259</td>
<td>148 (57.1%)</td>
<td>109 (42.1%)</td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>11.6% (8.0%-16.1%)</td>
<td>15.5% (10.1%-22.4%)</td>
<td>6.4% (2.6%-12.8%)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>2.0 months</td>
<td>2.1 months</td>
<td>2.0 months</td>
</tr>
<tr>
<td>Six-month PFS</td>
<td>14.1%</td>
<td>HR: 0.68 (95% CI: 0.52-0.88)</td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>5.6 months</td>
<td>5.8 months</td>
<td>4.6 months</td>
</tr>
<tr>
<td>Six-month OS</td>
<td>46.5%</td>
<td>PD-L1+ve vs. -ve</td>
<td></td>
</tr>
<tr>
<td>12-month OS</td>
<td>23.4%</td>
<td>HR: 0.76 (95% CI: 0.57-1.00)</td>
<td></td>
</tr>
</tbody>
</table>

Fuchs et al JAMA Oncol 2018; Kulangara et al Arch Pathol Lab Med 2018
PD-L1 Diagnostic Assays: Mess or Harmony

Substantially lighter in staining intensity

Scheel et al Mod Pathol 2016; Hirsch et al J Thorac Oncol 2017; Rimm et al JAMA Oncol 2017
Biomarkers for PD-1/PD-L1 antibodies

- IHC – which one? Which cut-off? 1%, 5%, 10%, 50%; Tumour cells or immune cells?
- Microsatellite instability
- EBV status
- T-cell inflamed gene expression profiling score
- Total Mutational burden (TMB)
# PD-1 antibody in metastatic MSI-high gastric cancer (~4% of patients)

<table>
<thead>
<tr>
<th>CHECKMATE 032&lt;sup&gt;1&lt;/sup&gt;</th>
<th>NIVO 3 (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MSI-H n = 7</td>
</tr>
<tr>
<td><strong>ORR, n (%)</strong></td>
<td>2 (29) [4, 71]</td>
</tr>
<tr>
<td><strong>DCR, n (%)</strong>&lt;sup&gt;†&lt;/sup&gt;</td>
<td>5 (71)</td>
</tr>
<tr>
<td><strong>12-month OS rate</strong></td>
<td>57%</td>
</tr>
<tr>
<td><strong>18-month OS rate</strong></td>
<td>29%</td>
</tr>
<tr>
<td><strong>Median DOR (95% CI), months</strong></td>
<td>10 (7, 13)</td>
</tr>
</tbody>
</table>

**KEYNOTE-059**<sup>2</sup>
Department of ORR
MSI-high 4/7 (57%)
non-MSI-high 15/167 (9%)

**KEYNOTE 061**<sup>3</sup>
Department of ORR
MSI-high 7/15 (47%)

<sup>1</sup>Janjigian et al J Clin Oncol 2018;
<sup>2</sup>Fuchs et al JAMA Oncol 2018;
<sup>3</sup>Shitara et al Lancet 2018
Biomarkers for PD-1/PD-L1 antibodies

• IHC – which one? Which cut-off? 1%, 5%, 10%, 50%; Tumour cells or immune cells?
• Microsatellite instability
• EBV status
• T-cell inflamed gene expression profiling score
• Total Mutational burden (TMB)
The Cancer Genome Atlas
oesophago-gastric cancer

The Cancer Genome Atlas Research Network; Nature 2017
Can treatment be tailored according to TCGA subtype?
EBV-infected/MSI gastric cancer

PD-L1 expression

Interferon-γ gene set enrichment

TI: tumour-infiltrating
IM: invasive margin

Derks et al Oncotarget 2016
EBV-associated and EBV-negative gastric cancer

<table>
<thead>
<tr>
<th></th>
<th>Total (n)</th>
<th>PD-L1 in cancer cells</th>
<th></th>
<th>PD-L1 in immune cells</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>P-value</td>
<td>Positive</td>
</tr>
<tr>
<td>EBV+GC</td>
<td>96</td>
<td>33 (34.4%)</td>
<td>63 (65.6%)</td>
<td></td>
<td>43 (44.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P-score 2: 26</td>
<td>P-score 0: 38</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>P-score 3: 7</td>
<td>P-score 1: 25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV-negative GC</td>
<td>136</td>
<td>6 (4.41%)</td>
<td>130 (95.6%)</td>
<td>&lt; 0.001*</td>
<td>37 (27.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P-score 2: 6</td>
<td>P-score 0: 74</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>P-score 3: 0</td>
<td>P-score 1: 56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLH1-negative</td>
<td>36</td>
<td>2 (5.6%)</td>
<td>34 (94.4%)</td>
<td></td>
<td>16 (44.4%)</td>
</tr>
<tr>
<td>Diffuse</td>
<td>50</td>
<td>3 (6.0%)</td>
<td>47 (94.0%)</td>
<td></td>
<td>9 (18.0%)</td>
</tr>
<tr>
<td>Intestinal</td>
<td>50</td>
<td>1 (2.0%)</td>
<td>49 (98.0%)</td>
<td></td>
<td>12 (24.0%)</td>
</tr>
</tbody>
</table>

Abbreviations: EBV, Epstein–Barr virus; EBV+GC, EBV-associated gastric cancer; GC, gastric cancer; PD-L1, programmed death-ligand 1; P-score, proportion score. *P < 0.05.

Saito et al Mod Pathol 2017
PD-L1 antibody in EBV+ve gastric cancer

- 61 patients treated with pembrolizumab
- 6/6 patients (100%) with EBV+ve gastric cancer had at least PR
Biomarkers for PD-1/PD-L1 antibodies

• IHC – which one? Which cut-off? 1%, 5%, 10%, 50%; Tumour cells or immune cells?
• Microsatellite instability
• EBV status
• T-cell inflamed gene expression profiling score
• Total Mutational burden (TMB)
KEYNOTE-059: T cell inflamed gene expression profiling score

Higher GEP score $\rightarrow$ better response (p=0.01)

Higher GEP score $\rightarrow$ better PFS (p=0.002)

Fuchs et al JAMA Oncol 2018
Biomarkers for PD-1/PD-L1 antibodies

- IHC – which one? Which cut-off? 1%, 5%, 10%, 50%; Tumour cells or immune cells?
- Microsatellite instability
- EBV status
- T-cell inflamed gene expression profiling score
- Total Mutational burden (TMB)
Lessons from NSCLC (TMB)

CheckMate-227

NSCLC
CTx naïve
No genetic alteration

PD-L1 <1%  N=550
PD-L1≥1%  N=1189

IPI+NIVO (N=139)
CTx  (N=160)

High TMB: defined as 10MT/Mb by Foundation One

HR 0.58 (95%CI. 0.41-0.81)  p<0.001

<table>
<thead>
<tr>
<th>High TMB</th>
<th>1Y-PFS</th>
<th>MST</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivo + Ipi</td>
<td>42.6%</td>
<td>7.2 M</td>
<td>5.5-13.2</td>
</tr>
<tr>
<td>CTx</td>
<td>13.2%</td>
<td>5.5 M</td>
<td>4.4-5.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low TMB</th>
<th>1Y-PFS</th>
<th>MST</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivo + Ipi</td>
<td>26%</td>
<td>3.2 M</td>
<td>2.7-4.3</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>17%</td>
<td>5.5 M</td>
<td>4.3-5.6</td>
</tr>
</tbody>
</table>

HR 1.07 (95%CI. 0.84-1.35)

Hellmann et al. N Engl J Med. 2018
TMB for G/GEJ Cancer, ASCO 2018

‘SCRUM JAPAN’ by OCP panel (143-gene platform)

MSK-IMPACT™ (468-gene platform)

Panel is possible instead of WES, but optimal ‘cut off’ is not established

Nakamura et al ASCO 2018

Gready et al ASCO 2018
Correlating tissue and ctDNA mutational load with PD-L1 antibody efficacy in gastric cancer

Kim et al Nat Med 2018
Biomarkers for PD-1/PD-L1 antibodies

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I wish I know how to optimally select patients
Acknowledgement

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