IMMUNOTHERAPY FOR GASTRIC CANCER
ESMO Gastric Cancer Preceptorship

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DISCLOSURES

- Astellas
- Servier
- Celgene
- BMS
- Five Prime Therapeutics
- Gritstone Oncology
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.

HOW IMMUNOGENIC ARE GASTRIC AND OESOPHAGEAL CANCER?

TMB and PD-L1 expression in relation to response to immune checkpoint blockade

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

TALK OUTLINE

- Immunotherapy biology
- Chemorefractory GC studies
- 2nd line GC studies
- 1st line GC studies
- Combinations
- Biomarkers
Anti-PD-1 therapy is superior to best supportive care in patient with chemorefractory GC (ATTRACTION 2)

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

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

Randomisation (2:1)

Nivolumab
3 mg/kg IV Q2W

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

Placebo

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

Patient Characteristics

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

ATTRACTION-02: response rates and duration

ORR 12%

Responses seen in PD-L1 positive and negative patients

Median time to response was 1.6m (1.4-7.0m)
Responses also seen as late at 7 months
NIVOLUMAB IN CHEMOREFRACTORY GASTRIC CANCER
ATTRACTION-02: updated survival results

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

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

Nivolumab led to a 38% reduction in the risk of death compared to BSC.
ATTRACTION-02: survival appears to be independent of PD-L1 status

**NIVOLUMAB IN CHEMOREFRACTORY GASTRIC CANCER**

14% tested population were PD-L1 positive

PD-L1 antibody 28-8 pharmDx assay

PD-L1 positivity was defined as staining in 1% or more of tumour cells.

Pembrolizumab in Chemorefractory Gastric Cancer

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

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

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

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

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

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

PEMBROLIZUMAB IN CHEMOREFRACTORY GASTRIC CANCER
KEYNOTE-059

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

Cohort 1
≥ 2 prior lines chemotherapy

Pembrolizumab
200 mg Q3W

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

Patient Characteristics (N=259)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</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>
</tr>
<tr>
<td>2 vs. 3 vs. ≥4</td>
<td>52% vs. 29% vs. 19%</td>
</tr>
</tbody>
</table>
PEMBROLIZUMAB IN CHEMOREFRACTORY GASTRIC CANCER

KEYNOTE-059

ORR 11.6%
9% in MSS

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

Most of the responses are early

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

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

Responses in PDL1 positive and negative patients, but more common in PDL1 positive
PEMBROLIZUMAB IN CHEMOREFRACTORY GASTRIC CANCER
KEYNOTE-059: ORR according to PD-L1 status and line of Tx

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

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

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

Licensing status

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

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

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

- **Stratification: Asia vs non-Asia**

- **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 in overall survival

PFS benefit favours chemotherapy

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

- Immunotherapy biology
- Chemorefractory GC studies
- 2nd line GC studies
- 1st line GC studies
- Combinations
- Biomarkers
Anti-PD-1 therapy is not superior to chemotherapy in 2L PD-L1 negative or PD-L1 CPS ≥1 GC (KEYNOTE 061)

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

KEYNOTE-061

Key eligibility criteria

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

Stratification factors

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

Endpoints

Primary: OS and PFS in the CPS ≥1 population

Critical analysis – paclitaxel + ramucirumab not used as comparator.
KEYNOTE-061: OS in CPS ≥1 population

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

Median (95% CI)

- Pembrolizumab: 9.1 mo (6.2–10.7)
- Paclitaxel: 8.3 mo (7.6–9.0)

Crossing curves means violation of the proportional hazards assumption
Small number of patients at the tail of the curve


<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Pembrolizumab</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>196</td>
<td>130</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>199</td>
<td>78</td>
</tr>
</tbody>
</table>

Overall survival, %

- Pembrolizumab: 27.1% at 12 months, 14.8% at 18 months
- Paclitaxel: 39.8% at 6 months, 25.7% at 12 months

No. at Risk
PEMBROLIZUMAB VS PACLITAXEL IN 2L GC PATIENTS
KEYNOTE-061: Progression free survival in CPS ≥1

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

**PEMBROLIZUMAB VS PACLITAXEL IN 2L GC PATIENTS**

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

### CPS < 1

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/Pts</td>
<td>87/99</td>
<td>86/96</td>
</tr>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>4.8 (3.9–6.1)</td>
<td>8.2 (6.8–10.6)</td>
</tr>
</tbody>
</table>

### MSI-H

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/Pts</td>
<td>34/53</td>
<td>46/55</td>
</tr>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>Not reached</td>
<td>8.1 (2-16.7)</td>
</tr>
</tbody>
</table>

### CPS ≥ 10

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/Pts</td>
<td>34/53</td>
<td>46/55</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**

## 2L ANTI-PD-1 IN OESOPHAGEAL CANCER

**KEYNOTE 181**

**Pembrolizumab**

- 200 mg IV Q3W for up to 35 cycles

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

### Baseline characteristics (ITT population)

<table>
<thead>
<tr>
<th>Characteristic, n</th>
<th>Pembrolizumab N=314</th>
<th>Chemotherapy N=314</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>63 (23–84)</td>
<td>62 (24–84)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>139 (44.3)</td>
<td>133 (42.4)</td>
</tr>
<tr>
<td>Male</td>
<td>273 (86.9)</td>
<td>271 (86.3)</td>
</tr>
<tr>
<td>Asia</td>
<td>121 (38.5)</td>
<td>122 (38.9)</td>
</tr>
<tr>
<td>Rest of World</td>
<td>193 (61.5)</td>
<td>192 (61.1)</td>
</tr>
<tr>
<td>ECOG PS 1</td>
<td>187 (59.6)</td>
<td>197 (62.7)</td>
</tr>
<tr>
<td>Squamous-cell carcinoma</td>
<td>198 (63.1)</td>
<td>203 (64.6)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>116 (36.9)</td>
<td>111 (35.4)</td>
</tr>
<tr>
<td>PD-L1 CPS ≥10</td>
<td>107 (34.1)</td>
<td>115 (36.6)</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>290 (92.4)</td>
<td>286 (91.1)</td>
</tr>
<tr>
<td>0-1 prior therapies</td>
<td>305 (97.1)</td>
<td>310 (98.7)</td>
</tr>
<tr>
<td>≥2 prior therapies</td>
<td>9 (2.9)</td>
<td>4 (1.3)</td>
</tr>
</tbody>
</table>

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

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

ITT analysis was also negative for OS benefit
2L ANTI-PD-1 IN OESOPHAGEAL CANCER

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

Statistically significant benefit in terms of OS for CPS ≥ 10 patients meeting co-primary endpoint

2L ANTI-PD-1 IN OESOPHAGEAL CANCER
KEYNOTE 181: Overall Survival subgroup analysis

Subgroup analysis reveals effect of histology and ethnicity even in high PD-L1 expressing tumours
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)
Pts with recurrent or metastatic gastric or GEJ adenocarcinoma; ECOG PS 0/1; HER2/neu negative*; no prior PD-1/PD-L1 tx)

KN059 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

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

OS
Median (95% CI) 13.8 (8.6–NR)
6-mo rate 76.0%

ORR

| All patients | 60% |
| PD-L1 positive | 69% |
| PD-L1 negative | 38% |

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

Pembrolizumab 200 mg Q3W for up to 35 cycles
Pembrolizumab 200 mg Q3W (to 35 cycles) + Chemotherapy
Placebo + Chemotherapy

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

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

Tabernero et al, ASCO 2019
KEYNOTE-062
Statistical considerations

Overall alpha for study was controlled at one-sided 2.5% across all comparisons

- Hypotheses in top row tested first and in parallel
  - Remaining hypotheses tested only if preceding hypothesis was positive
  - Prespecified analysis plan allowed alpha passing from successful hypotheses
- Final analysis: planned to occur ≥22 months after last patient was randomized and ~415 OS events observed in P+C and C treatment groups in patients with PD-L1 CPS ≥1

*Alpha passed from non-inferiority to superiority test; Median follow-up, 11.3 months (range, 0.2-41.2); Data cutoff: March 26, 2019.
# 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><strong>Age, median (range), years</strong></td>
<td>61.0 (20-83)</td>
<td>62.0 (22-83)</td>
<td>62.5 (23-87)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>180 (70)</td>
<td>195 (76)</td>
<td>179 (72)</td>
</tr>
<tr>
<td><strong>ECOG PS 1</strong></td>
<td>125 (49)</td>
<td>138 (54)</td>
<td>135 (54)</td>
</tr>
<tr>
<td><strong>Metastatic disease</strong></td>
<td>245 (96)</td>
<td>243 (95)</td>
<td>235 (94)</td>
</tr>
<tr>
<td><strong>CPS ≥10</strong></td>
<td>92 (36)</td>
<td>99 (39)</td>
<td>90 (36)</td>
</tr>
<tr>
<td><strong>MSI-H</strong></td>
<td>14 (5)</td>
<td>17 (7)</td>
<td>19 (8)</td>
</tr>
<tr>
<td><strong>Region</strong></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><strong>Primary tumor location</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>176 (69)</td>
<td>170 (66)</td>
<td>181 (72)</td>
</tr>
<tr>
<td>GEJ</td>
<td>79 (31)</td>
<td>85 (33)</td>
<td>67 (27)</td>
</tr>
<tr>
<td><strong>Backbone therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-FU</td>
<td>-</td>
<td>98 (38)</td>
<td>95 (38)</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>-</td>
<td>159 (62)</td>
<td>155 (62)</td>
</tr>
</tbody>
</table>

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

Tabernero et al, ASCO 2019

Event | HR (99.2% CI) | NI
--- | --- | ---
Pembro | 79% | 0.91 | 1.2
Chemo | 86% | (0.69-1.18) |

12-mo rate: 47% (Pembro) vs 46% (Chemo)
24-mo rate: 27% (Pembro) vs 19% (Chemo)
Median (95% CI): 10.6 mo (7.7-13.8) (Pembro) vs 11.1 mo (9.2-12.8) (Chemo)

\[a\] NI, non-inferiority margin; \[b\] 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

Data cutoff: March 26, 2019
Tabernero et al, ASCO 2019
KEYNOTE 062

Pembrolizumab vs chemotherapy in PFS results

Most patients treated with pembrolizumab progress quickly regardless of CPS status

Tabernero et al, ASCO 2019
KEYNOTE 062

Pembrolizumab vs chemotherapy radiological response and duration of response

Radiological response rates are less for pembrolizumab than chemotherapy regardless of CPS status
Responses to pembrolizumab are more long lived

Tabernero et al, ASCO 2019
KEYNOTE 062
Pembrolizumab plus chemotherapy vs chemotherapy OS results CPS ≥1

Pembrolizumab plus chemotherapy was not superior to chemotherapy alone

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

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

Negative interaction between chemotherapy and effect of pembrolizumab in immunogenic tumours?
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 ORR and duration of response

ORR is improved in chemotherapy plus pembrolizumab patients compared to chemotherapy alone
KEYNOTE 062
Pembrolizumab plus chemotherapy vs chemotherapy PFS results

Chemotherapy plus pembrolizumab equivalent PFS outcomes in CPS ≥1 and CPS ≥10 patients
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, combination chemotherapy plus pembrolizumab modestly improved radiological response rates and PFS compared to chemotherapy, but did not improve overall survival.

Impact of other biomarkers such as TMB need to be explored.
TALK OUTLINE

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

There are many, results are mostly preliminary

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

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

- Immunotherapy biology
- Chemorefractory GC studies
- 2nd line GC studies
- 1st line GC studies
- Combinations
- Biomarkers
HOW IMMUNOGENIC ARE GASTRIC AND OESOPHAGEAL CANCER?
TMB and PD-L1 expression in relation to response to immune checkpoint blockade

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

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

**MSI**

**KEYNOTE-061**

![Graph showing overall survival (%)]

- **MSI-H 2.4% mGC**

**PD-L1 CPS >10**

**KEYNOTE-061 & KEYNOTE-062**

![Graph showing overall survival (%)]

- **15-18% mGC screened**

### IMMUNE ENVIRONMENT IN A HETEROGENEOUS DISEASE

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

GASTRIC CANCER IMMUNE ENVIRONMENT

In TGCA dataset CIN tumours have lowest INF\(\gamma\) signature

Specific mutations associated with inflamed subtype: \textit{PIK3CA, ATM, RHOA} and \textit{CDH1}

Amplifications associated with immune ignorance: \textit{ERBB2, MYC, VEGFA}

GC-CIN tumours have the lowest proportion of T-cell inflamed tumours
Immunotherapy for gastroesophageal cancer

Conclusions

- Anti-PD-1 therapy is a validated standard for patients with chemorefractory gastroesophageal cancer
  - Single agent activity is modest; anti-PD-L1 not superior to chemotherapy

- Second line monotherapy trials in highly enriched populations (predominantly SCC) show promise

- First line – 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.

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