Advances in gastric cancer: Biology and Treatment for advanced disease

Andrés Cervantes
Professor of Medicine
Outline

- Molecular classification
  - Pathology
  - Classification after gene expression
  - The Cancer Genome Atlas Research Network
  - Molecular differences between Asian and Western patients

- Treatment for advanced disease
  - First line
  - Second line

- Targeted therapies
- Immunotherapy
Classification of gastric adenocarcinoma: Pathology

- Intestinal versus diffuse subtypes

Classification of gastric adenocarcinoma: Pathology

- Papillary carcinomas
- Tubular carcinomas
- Mucinous carcinomas
- Poorly cohesive carcinomas

WHO Classification of Tumours of the Digestive System 4th Ed.2010 (International Agency for Cancer Research)
Classification of gastric adenocarcinoma: Gene expression

- Consensus hierarchical clustering with iterative feature selection
- Classification set: 248 gastric adenocarcinomas
- Validation set: 70 gastric adenocarcinomas

- Three molecular subtypes:
  - Proliferative
  - Metabolic
  - Mesenchymal

Classification of gastric adenocarcinoma: Gene expression

Classification of gastric adenocarcinoma: Gene expression

Metabolic GC cell lines show sensitivity to 5-Fluorouracil treatment *in vitro*
GC patients with metabolic subtype tumours respond better to 5-Fluorouracil treatment

Note: Patients with more severe disease were more often treated with 5-FU

P-value for interaction = 0.0012

Mesenchymal GC lines are sensitive to PIK3CA inhibitors (high throughput drug screening)

Screening performed by experimental therapeutics centre, A-star

Classification of gastric adenocarcinoma: Gene expression and relation to 5FU sensitivity

Classification of gastric adenocarcinoma: Gene expression and relation to 5FU sensitivity

Comprehensive molecular characterisation of gastric adenocarcinoma: Molecular platforms

- Array-based somatic copy number analysis
- Whole exome sequencing
- Array-based DNA methylation profiling
- Messenger RNA sequencing
- MicroRNA sequencing
- Reverse Phase Protein Array (RPPA)

Comprehensive molecular characterisation of gastric adenocarcinoma: Molecular platforms

227 tumours

EBV (EBV-CIMP)

MSI high

GS (genomically stable)

CIN (chrom instability)
Comprehensive molecular characterisation of gastric adenocarcinoma: PI3KCA mutations by subtype

Comprehensive molecular characterisation of gastric adenocarcinoma: The ACRG approach

Comprehensive molecular characterisation of gastric adenocarcinoma: The ACRG approach predicts survival
Molecular signatures of tumour immunity may distinguish between Asian versus non-Asian gastric cancers

Molecular signatures of tumour immunity may distinguish between Asian versus non-Asian gastric cancers

Study schematic diagram

9 expression profiling studies (n=1,016)
- 6 studies of Asian origin (n = 890)
- 3 studies of non-Asian origin (n = 126)

Stage 1

4 Affymetrix platform studies
- 2 studies of Asian origin (n = 207)
- 2 studies of non-Asian origin (n = 92)

Stage 2

5 non Affymetrix platform studies
- 4 studies of Asian origin (n = 683)
- 1 study of non-Asian origin (n = 34)

Validation analyses

Immunohistochemistry assessment in tissue microarray studies
- 1 study of Asian origin (n = 219); Japanese cohort
- 1 study of non-Asian origin (n = 446); Caucasian cohort

Molecular signatures of tumour immunity may distinguish between Asian \textit{versus} non-Asian gastric cancers

Molecular signatures of tumour immunity may distinguish between Asian versus non-Asian gastric cancers.
Outline

- Treatment for advanced disease
  - First line
  - Second line
- Targeted therapies
- Immunotherapy
Treatment for advanced gastric cancer: What is standard of care? ESMO guidelines

- Surgery
  - Re-assess
  - HER-2 negative
    - Platinum+ fluoropyrimidine-based doublet or triplet regimen
  - HER-2 positive
    - Trastuzumab + CF/CX
  - Palliative chemotherapy
  - 2nd line chemo
    - Clinical trials if adequate PS
  - Best supportive care if unfit for treatment
  - Inoperable or metastatic

Treatment for metastatic/unresectable gastric cancer: Active agents in first line

- Based upon superiority trials:
  - 5-FU
  - Cisplatin
  - Docetaxel
  - Trastuzumab

- Based upon non-inferiority trials
  - Oxaliplatin
  - Capecitabine
  - S1
  - Irinotecan

Have we made any progress in the treatment of advanced gastric cancer?

- **Transtuzumab + CDDP + FU or Cape**
  - Median OS: 13.8 months

- **EOX**
  - Median OS: 11.2 months

- **5-FU + LV + Oxaliplatin (FLO)**
  - Median OS: 10.7 months

- **Capecitabine + Cisplatin (XP)**
  - Median OS: 10.5 months

- **Docetaxel + Cisplatin + 5-FU**
  - Median OS: 9.2 months

- **5-FU monotherapy**
  - Median OS: 7 months

- **BSC**
  - Median OS: 4 months

**MEDIAN OVERALL SURVIVAL IN ADVANCED GASTRIC CANCER**


BSC: Best supportive care; CDDP, cisplatin; EOX: Epirubicin/Oxaliplatin/Capecitabine; 5-FU, 5-fluorouracil.
Have we made any progress in the treatment of advanced gastric cancer?

**Combination vs monotherapy**
- Transtuzumab + CDDP + FU/Cape
  - HR: 0.74 p=0.0046
- EOX
  - HR: 0.80 p=0.02
- FLO
  - HR: Not shown p=0.506
- XP
  - HR: 0.85 p=0.008
- DCF
  - HR: 0.77 p=0.02

**5-FU monotherapy vs BSC**
- Combination vs monotherapy
  - HR: 0.83 p=0.001
- 5-FU monotherapy vs BSC
  - HR: 0.39 p<0.00001

**RISK OF DEATH REDUCTION IN ADVANCED GASTRIC CANCER**


EOX: Epirubicin/Oxaliplatin/Capecitabine; FLO: 5-FU/leucovorin/Oxaliplatin; XP: Capecitabine/CDDP. CDDP, cisplatin; DCF: Docetaxel/CDDP/5-FU; BSC: Best supportive care.
FFCD-GERCOR-FNCLCC 03-07 Phase III Study. FOLFIRI vs. ECF in advanced gastric cancer

Stratification:
- Measurable or not
- PS \(\text{WHO} \) 0-1 or 2
- Adj (R)CT or not
- Linitis or not
- Cardial or gastric
- Center

A: ECX until progression; then FOLFIRI 2d line
B: FOLFIRI until progression; then ECX 2d line

ECX: D1 = Epirubicin 50 mg/m² (15 min.), Cisplatin 60 mg/m² (1 h); D2 to 15: Capecitabine 1 g/m² x 2/d. D1 = D21. *Cumulated dose of Epirubicin < 900 mg/m² (max 18 cures)*

FOLFIRI: D1 = Irinotecan 180 mg/m² (90 min) + LV 400 mg/m² (2h), 5FU b 400 mg/m², 5FU c.i. 2400 mg/m² (46h). D1 = D14

- **Objective I:** 1\(^{\text{st}}\) line Time-to-Treatment Failure (TTF)
- **Objectives II:**
  - PFS, OS, (TTF 2\(^{\text{nd}}\) line)
  - Toxicity
  - Response rate, QoL

Objective I: 1st line Time-to-Treatment Failure (TTF)

ECX arm: Epirubicin, cisplatin, and capecitabine as the first-line treatment.
FOLFIRI arm: Irinotecan, leucovorin, fluorouracil bols, and continuous infusion as the first-line treatment.

**Objective II:** Response Rate (RR), PFS and OS

<table>
<thead>
<tr>
<th></th>
<th>ECF N=209</th>
<th>FOLFIRI n=207</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RR 1\textsuperscript{st}</strong></td>
<td>39.2%</td>
<td>37.8%</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>RR 2\textsuperscript{nd}</strong></td>
<td>10.1%</td>
<td>13.7%</td>
<td></td>
</tr>
<tr>
<td><strong>PFS (months)</strong></td>
<td>5.29</td>
<td>5.75</td>
<td>0.96</td>
</tr>
<tr>
<td>Median range</td>
<td>4.53-6.31</td>
<td>5.19-6.74</td>
<td></td>
</tr>
<tr>
<td><strong>OS (months)</strong></td>
<td>9.49</td>
<td>9.72</td>
<td>0.95</td>
</tr>
<tr>
<td>Median range</td>
<td>8.77-11.14</td>
<td>8.54-11.27</td>
<td></td>
</tr>
</tbody>
</table>

# Targeted therapies in first-line treatment for advanced gastric cancer: Summary of Phase III Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Chemotherapy</th>
<th>Biological</th>
<th>HR OS</th>
<th>P value</th>
<th>Increase in median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>ToGA&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Cisplatin+5-FU/capecitabine</td>
<td>Trastuzumab</td>
<td>0.74</td>
<td>0.04</td>
<td>+2.8 months</td>
</tr>
<tr>
<td>AVAGAST&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Cisplatin+capecitabine</td>
<td>Bevacizumab</td>
<td>0.87</td>
<td>0.10</td>
<td>+2.0 months</td>
</tr>
<tr>
<td>EXPAND&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Cisplatin+capecitabine</td>
<td>Cetuximab</td>
<td>1.00</td>
<td>0.95</td>
<td>-1.3 months</td>
</tr>
<tr>
<td>REAL-3&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Oxaliplatin+epirubicin+capecitabine</td>
<td>Panitumumab</td>
<td>1.37</td>
<td>0.013</td>
<td>-2.5 months</td>
</tr>
<tr>
<td>RILOMET-1&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Cisplatin+epirubicin+capecitabine</td>
<td>Rilotumumab</td>
<td>--</td>
<td>--</td>
<td>Stopped in futility analysis</td>
</tr>
<tr>
<td>METGASTRIC&lt;sup&gt;6&lt;/sup&gt;</td>
<td>FOLFOX6</td>
<td>Onartuzumab</td>
<td>1.06</td>
<td>0.83</td>
<td>-0.6 months</td>
</tr>
</tbody>
</table>

Structure and activation of the HER2 and HER3 receptors

Targeted therapies against HER2 in advanced gastric cancer: Summary of Phase III Trials on lapatinib

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>Chemotherapy backbone</th>
<th>Line of therapy number</th>
<th>HR OS</th>
<th>P value</th>
<th>Response rate</th>
<th>Increase in median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>ToGA¹</td>
<td>Cisplatin+5-FU/capecitabine</td>
<td>First 584</td>
<td>0.74</td>
<td>0.04</td>
<td>51% vs. 37% p=0.0017</td>
<td>+2.8 months</td>
</tr>
<tr>
<td>LOGiC²</td>
<td>Oxaliplatin/capecitabine</td>
<td>First 545</td>
<td>0.91</td>
<td>0.35</td>
<td>53% vs. 40% p=n.s.</td>
<td>+1.7 months</td>
</tr>
<tr>
<td>TyTAN³</td>
<td>Paclitaxel</td>
<td>Second 261</td>
<td>0.84</td>
<td>0.20</td>
<td>27% vs. 9% p=0.001</td>
<td>+2.1 months</td>
</tr>
</tbody>
</table>

Key discoveries in advanced gastric cancer

- **CT + BSC is superior to BSC (Ref 4,5,8)**
- **ECF is superior to FAMTX (Ref 17)**
- **DCF is superior to CF (Ref 35)**
- **Poli-CT regimens superior vs single agent (Ref 7)**
- **Cisplatin+S1 is superior to S1 (Ref 24)**
- **Trastuzmab + CF is superior to CF in HER2+ (Ref 43)**
- **Oxaliplatin is no inferior to cisplatin (Ref 18,29)**
- **S1 is a valuable option to 5FU (Ref 26)**
- **Capecitabine is non inferior to 5FU (Ref 18,20)**
- **Survival benefit of 2nd line CT vs BSC (Ref 53,54)**

## Gastric cancer: Second line chemotherapy. Trials comparing BSC versus active treatment

<table>
<thead>
<tr>
<th>Trial author</th>
<th>Year</th>
<th>Patients random (n)</th>
<th>Treatment</th>
<th>Response rate (%)</th>
<th>HR OS</th>
<th>P value</th>
<th>Gain in median survival</th>
</tr>
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<tbody>
<tr>
<td>Thuss-Patience, et al.¹</td>
<td>2011</td>
<td>40 1:1</td>
<td>Irinotecan</td>
<td>NR SD 58%</td>
<td>0.48</td>
<td>0.0023</td>
<td>2.4 months</td>
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<tr>
<td>Kang, et al.²</td>
<td>2012</td>
<td>193 2:1</td>
<td>Irinotecan Docetaxel</td>
<td>NR</td>
<td>0.65</td>
<td>0.004</td>
<td>1.3 months</td>
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<tr>
<td>Ford, et al.³</td>
<td>2014</td>
<td>168 1:1</td>
<td>Docetaxel</td>
<td>NR</td>
<td>0.67</td>
<td>0.01</td>
<td>1.6 months</td>
</tr>
</tbody>
</table>

Gastric cancer second line chemotherapy: Docetaxel vs. BSC (COUGAR-02 Trial)

**Arm A:** Best Supportive Care

**Arm B:** Docetaxel 75 mg/m² every 3 weeks up to 6 courses

**Main aim: Overall survival**

- Stratification by:
  - Locally advanced vs. metastatic
  - Site: Oesophagus vs. junction vs. gastric
  - Response to previous chemotherapy: No vs. < or > than 3 months
  - Performance status 0–1 vs. 2

- 164 patients needed to show a HR of 0.64 in favour of chemotherapy with two-sided alfa 0.05 and 80% power

Gastric cancer second line chemotherapy: Docetaxel vs. BSC (COUGAR-02 Trial) is improving survival
Gastric cancer second line chemotherapy: Docetaxel vs. BSC (COUGAR-02 Trial) is improving all subgroups

Figure 3: Hazard ratio plot of the treatment effect by prognostic factors for overall survival
ECOG PS = Eastern Cooperative Oncology Group performance status.
Gastric cancer second line chemotherapy: Docetaxel vs. BSC (COUGAR-02 Trial) is improving QOL

Figure 4: Health-related quality of life (HRQL) outcomes. Positive values in function scale and negative values for the symptom scale denote benefit from docetaxel compared with active symptom control.

### Gastric cancer: Second line chemotherapy trials comparing BSC versus active treatment

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<td>2014</td>
<td>168 1:1</td>
<td>Docetaxel</td>
<td>0.67</td>
<td>0.01</td>
<td>1.6 months</td>
</tr>
<tr>
<td>Otshu, <em>et al.</em>&lt;sup&gt;4&lt;/sup&gt;</td>
<td>2013</td>
<td>656 2:1</td>
<td>Everolimus</td>
<td>0.90</td>
<td>0.124</td>
<td>0.9 months</td>
</tr>
<tr>
<td>Fuchs, <em>et al.</em>&lt;sup&gt;5&lt;/sup&gt;</td>
<td>2014</td>
<td>355 2:1</td>
<td>Ramucirumab</td>
<td>0.77</td>
<td>0.047</td>
<td>1.4 months</td>
</tr>
</tbody>
</table>

**Clinical anti-VEGF pathway therapies**

- **Soluble receptors** (VEGF Trap, aflibercept)
- **Anti-VEGFR MAbs** (IMC-1C11, Ramucirumab)
- **Tyrosine kinase inhibitors (TKIs)** (regorafenib, SU5416, SU6668, sunitinib, vatalanib, sorafenib, cediranib, AEE788, AMG-706, KRN-951)
- **Anti-VEGF MAbs** (bevacizumab)
- **Anti-PIGF MAbs** (TB-403)
- **Ribozymes**

**Signal transduction**

Main aim: Overall survival

- Stratification by:
  - Weight Loss: < or > 10%
  - Site: Oesophagus vs. junction vs. gastric
  - Geographic region

- 615 patients needed to show a HR of 0.71 in favour of ramucirumab with two-sided alfa 0.05 and 90% power

Arm A: Best Supportive Care/Placebo

Arm B: Ramucirumab 8 mg/kg every 2 weeks

2:1
Gastric cancer second line treatment: Ramucirumab vs. BSC (REGARD Trial) is improving survival
Gastric cancer second line treatment: Ramucirumab vs. BSC (REGARD Trial) is improving disease control

<table>
<thead>
<tr>
<th></th>
<th>Ramucirumab (n=238)</th>
<th>Placebo (n=117)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Partial response</td>
<td>7 (3%)</td>
<td>3 (3%)</td>
<td>-</td>
</tr>
<tr>
<td>Stable disease</td>
<td>108 (45%)</td>
<td>24 (21%)</td>
<td>-</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>78 (33%)</td>
<td>63 (54%)</td>
<td>-</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>44 (18%)</td>
<td>27 (23%)</td>
<td>-</td>
</tr>
<tr>
<td>Objective response</td>
<td>8 (3%)</td>
<td>3 (3%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Disease control rate*</td>
<td>116 (49%)</td>
<td>27 (23%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are n (%), unless otherwise indicated. *Denotes best response for complete response, partial response or stable disease.
Gastric cancer second line treatment: Ramucirumab vs. BSC (REGARD Trial) delays deterioration

Figure 6: Time to deterioration in ECOG performance status to a score of 2 or worse
HR=hazard ratio. ECOG=Eastern Cooperative Oncology Group.
## Gastric cancer: Second line chemotherapy trials comparing two active treatments

<table>
<thead>
<tr>
<th>Trial author</th>
<th>Year</th>
<th>Patients (n)</th>
<th>Treatment</th>
<th>HR OS</th>
<th>P value</th>
<th>Gain in median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hironaka, et al.¹</td>
<td>2013</td>
<td>223</td>
<td>Irinotecan vs. paclitaxel</td>
<td>1.13</td>
<td>0.38</td>
<td>0.9 months for irinotecan</td>
</tr>
<tr>
<td>Wilke et al.²</td>
<td>2014</td>
<td>665</td>
<td>Paclitaxel+/-ramucirumab</td>
<td>0.80</td>
<td>0.017</td>
<td>2.2 months</td>
</tr>
</tbody>
</table>

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Gastric cancer second line treatment: Paclitaxel+/-ramucirumab (Rainbow Trial)

**Main aim: Overall survival**
- **Stratification by:**
  - Measurable vs. non-measurable
  - Time to progression after first line: < or > 6 month
  - Geographic region
- **663 patients needed to show a HR of 0.75 in favour of paclitaxel+ramucirumab with two-sided alfa 0.05 and 90% power**

**Arm A:** Paclitaxel 80 mg/m² day 1, 8, 14 every 28 days plus Placebo

**Arm B:** Paclitaxel 80 mg/m² day 1, 8, 14 every 28 days Ramucirumab 8 mg/kg every 2 weeks
Gastric cancer second line treatment: Addition of ramucirumab to paclitaxel improves overall survival (Rainbow Trial)

**Gastric cancer second line treatment: Addition of ramucirumab to paclitaxel improves response rate (Rainbow Trial)**

<table>
<thead>
<tr>
<th>Best overall response</th>
<th>Ramucirumab plus paclitaxel (N=330)</th>
<th>Placebo plus paclitaxel (N=335)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>2 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>90 (27%)</td>
<td>53 (16%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>172 (52%)</td>
<td>159 (47%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>43 (13%)</td>
<td>83 (25%)</td>
</tr>
<tr>
<td>Not evaluable or not assessed</td>
<td>23 (7%)</td>
<td>39 (12%)</td>
</tr>
</tbody>
</table>

Data are number (%) or number (%; 95% CI), unless otherwise indicated.

Gastric cancer second line treatment: Addition of ramucirumab to paclitaxel is tolerable (Rainbow Trial)

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Ramucirumab plus paclitaxel (n=327)</th>
<th>Placebo plus paclitaxel (n=329)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Bleeding or haemorrhage</td>
<td>123 (38%)</td>
<td>12 (4%)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>51 (16%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Liver injury or failure</td>
<td>39 (12%)</td>
<td>12 (4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34 (10%)</td>
<td>48 (15%)</td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage</td>
<td>21 (6%)</td>
<td>10 (3%)</td>
</tr>
</tbody>
</table>

Background of apatinib

- Apatinib (YN968D1)\(^1\)
  - A new small molecular tyrosine kinase inhibitor that highly and selectively inhibits the VEGFR2
  - The MTD is determined to be 850 mg/day administered orally

- Phase I / IIa study (N=65)\(^1\)
  - CR: 1.54%, PR: 12.31%, SD: 66.15%
  - DCR: 80.00%
  - PD: 20.00%

Apatinib in a Phase III Study design vs. placebo

- **Design:** Multicenter, randomised, double-blind, placebo-controlled clinical trial

- **1 treatment cycle = 28 days**
- **Stratification factor:** Number of metastatic sites (≤ 2 vs. >2)

Apatinib improves survival in third line for advanced gastric cancer

Overall survival of FAS population

__Survival probability__

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>mOS (95% CI), months</th>
<th>P value</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apatinib</td>
<td>176</td>
<td>6.5 (4.8–7.6)</td>
<td>0.0149</td>
<td>0.709</td>
</tr>
<tr>
<td>Placebo</td>
<td>91</td>
<td>4.7 (3.6–5.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PD-1 pathway and immune surveillance

- PD-1 is a negative co-stimulatory receptor expressed primarily on activated T cells¹
- Binding of PD-1 to its ligands PD-L1 and PD-L2 inhibits effector T-cell function¹
- Expression of PD-L1 on tumour cells and macrophages can suppress immune surveillance and permit neoplastic growth²


Courtesy of Muro K, et al. ASCO GI 2015; Abstract nr.03
Pembrolizumab (MK-3475) is a humanised IgG4, high-affinity, anti-PD-1

- Dual blockade of PD-L1 and PD-L2
- No cytotoxic (ADCC/CDC) activity
- Pharmacokinetics support dosing every 2 weeks (Q2W) or every 3 weeks (Q3W)
- Low occurrence of anti-drug antibodies, which have no impact on pharmacokinetics
- Demonstrated clinical activity in multiple tumour types\(^1\)–\(^7\)
- Recently approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor

KEYNOTE-012: Gastric cancer cohort

- **Screening:** 65 of 162 (40%) patients assessed for PD-L1 expression had PD-L1-positive tumours
- **Patients:** 19 patients from Asia and 20 patients from the rest of the world
- **Treatment:** 10 mg/kg IV Q2W
- **Response assessment:** Performed every 8 weeks per RECIST v1.1

**Pembrolizumab 10 mg/kg Q2W**

- Complete response → Discontinuation permitted
- Partial response or stable disease → Treat for 24 months or until progression or intolerable toxicity
- Confirmed progressive disease → Discontinue

**Notes:**

- a: Recurrent or metastatic adenocarcinoma of the stomach or GEJ
- b: ECOC PS 0-1
- c: PD-L1-positive tumour
- d: No systemic steroid therapy
- e: No autoimmune disease (active or history of)
- f: No active brain metastases

Courtesy of Muro K, *et al.* ASCO GI 2015; Abstract nr.03
PD-L1 expression in gastric cancer samples

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

Courtesy of Muro K, et al. ASCO GI 2015; Abstract nr.03
Pembrolizumab induces responses in chemorefractory gastric cancer

<table>
<thead>
<tr>
<th></th>
<th>Investigator review</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N = 36</td>
</tr>
<tr>
<td></td>
<td>22.2 (10.1, 39.2)</td>
</tr>
<tr>
<td></td>
<td>33.3 (19.1, 50.2)</td>
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<tr>
<td>ORR, % (95% CI)</td>
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<tr>
<td>Best overall response, n (%)</td>
<td></td>
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<tr>
<td>Complete response$^b$</td>
<td>0</td>
</tr>
<tr>
<td>Partial response$^b$</td>
<td>8 (22.2)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>5 (13.9)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>19 (52.8)</td>
</tr>
<tr>
<td>No assessment$^c$</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Not determined$^d$</td>
<td>3 (8.3)</td>
</tr>
</tbody>
</table>

Courtesy of Muro K, et al. ASCO GI 2015; Abstract nr.03
Maximum percentage change from baseline in tumour size\textsuperscript{a} KEYNOTE-012 (RECIST v1.1, Central Review)

Change from baseline in sum of longest diameter of target lesion, %

53.1%

Courtesy of Muro K, \textit{et al.} ASCO GI 2015; Abstract nr.03
64-year-old male with recurrent gastric cancer treated with pembrolizumab

March 22, 2014

May 8, 2014

July 3, 2014

August 28, 2014

September 26, 2014

November 6, 2014

Courtesy of Muro K, et al. ASCO GI 2015; Abstract nr.03
KEYNOTE-059: Phase 2 Study of Pembrolizumab for advanced gastric or GEJ adenocarcinoma

- Primary end point: ORR per RECIST v1.1 by central review

**COHORT 1**
- PD-L1⁺ or PD-L1⁻
- ≥2 prior treatments
- N = 180<sup>a</sup>

- Pembrolizumab 200 mg Q3W

**COHORT 2**
- PD-L1⁺ or PD-L1⁻
- No prior therapy
- N = 40<sup>b</sup>

- Pembrolizumab 200 mg + Cisplatin + 5FU, all Q3W

**COHORT 3**
- PD-L1⁺ only
- No prior therapy
- N = 50

- Pembrolizumab 200 mg Q3W

Courtesy of Muro K, *et al.* ASCO GI 2015; Abstract nr.03
Gastric cancer: Conclusions I

- Her2 status to be determined in all patients with advanced disease
- Trastuzumab to be added if HER2 positive (+++)
- Platinum-based chemotherapy as first option, with FOLFIRI as an alternative
- Second line chemotherapy also prolongs survival in good PS patients
- Ramucirumab as single agent prolongs survival versus BSC
- Ramucirumab in combination with paclitaxel improves outcomes over paclitaxel
Most targeted therapies failed in molecularly unselected trials
Immunotherapy (Pembrolizumab) under development with interesting data to be confirmed
Better selection of patients needed in clinical trials
Validation of molecular classification in trials
International cooperation
THANK YOU!