Systemic Therapy for Metastatic Gastric Cancer

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Disclosures

• Received honorariums from Roche, Lilly, Amgen, Leo and Bayer for consultant work
• Received travel support from Bayer
Outline

• Chemotherapy backbone options
• Role of biologics
• Update on clinical trials

Original Article

Capecitabine and Oxaliplatin for Advanced Esophagogastriac Cancer


Table 2. Analysis of Efficacy (Intention-to-Treat Population).  

<table>
<thead>
<tr>
<th>Variable</th>
<th>ECF (N = 263)</th>
<th>ECX (N = 250)</th>
<th>EOF (N = 245)</th>
<th>EOX (N = 244)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>225</td>
<td>213</td>
<td>213</td>
<td>199</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.92 (0.76–1.11)</td>
<td>0.96 (0.79–1.15)</td>
<td>0.80 (0.66–0.97)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.39</td>
<td>0.61</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median — mo</td>
<td>9.9</td>
<td>9.9</td>
<td>9.3</td>
<td>11.2</td>
</tr>
<tr>
<td>At 1 yr — % (95% CI)</td>
<td>37.7 (31.8–43.6)</td>
<td>40.8 (34.7–46.9)</td>
<td>40.4 (34.2–46.5)</td>
<td>46.8 (40.4–52.9)</td>
</tr>
<tr>
<td><strong>Progression-free survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median — mo</td>
<td>6.2</td>
<td>6.7</td>
<td>6.5</td>
<td>7.0</td>
</tr>
<tr>
<td>Patients who had progression or died</td>
<td>237</td>
<td>231</td>
<td>221</td>
<td>213</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.98 (0.82–1.17)</td>
<td>0.97 (0.83–1.17)</td>
<td>0.85 (0.70–1.02)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.80</td>
<td>0.77</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall — % (95% CI)†</td>
<td>40.7 (34.5–46.8)</td>
<td>46.4 (40.0–52.8)</td>
<td>42.4 (36.1–48.8)</td>
<td>47.9 (41.5–54.3)</td>
</tr>
<tr>
<td>Complete — %</td>
<td>4.1</td>
<td>4.2</td>
<td>2.6</td>
<td>3.9</td>
</tr>
<tr>
<td>Partial — %</td>
<td>36.6</td>
<td>42.2</td>
<td>39.8</td>
<td>44.0</td>
</tr>
<tr>
<td>P value</td>
<td>0.20</td>
<td>0.69</td>
<td>0.11</td>
<td></td>
</tr>
</tbody>
</table>
Fig 1. CONSORT diagram. ECX, epirubicin, cisplatin, and capecitabine; FOLFIRI, irinotecan, leucovorin, fluorouracil bolus, and continuous infusion.

Fig 2. Time-to-treatment failure (TTF) according to treatment arm (Kaplan-Meier estimation). ECX arm: epirubicin, cisplatin, and capecitabine as the first-line treatment, FOLFIRI arm: irinotecan, leucovorin, fluorouracil bolus, and continuous infusion as the first-line treatment. HR, hazard ratio.
Table 2. Efficacy Results for PFS and OS

<table>
<thead>
<tr>
<th></th>
<th>ECX Arm (n = 201)</th>
<th></th>
<th>FOLFOXIRI Arm (n = 271)</th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>95% CI</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>PFS, months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>5.29</td>
<td></td>
<td>4.53-6.31</td>
<td>5.35</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>5.03</td>
<td>2.46 to 8.07</td>
<td></td>
<td>5.00</td>
<td>2.76</td>
</tr>
<tr>
<td>OS, months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>9.40</td>
<td></td>
<td>8.77-11.14</td>
<td>9.72</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>11.17</td>
<td>7.03 to 16.35</td>
<td></td>
<td>10.71</td>
<td>6.51</td>
</tr>
</tbody>
</table>

Abbreviations: ECX, epirubicin, cisplatin, and capecitabine; FOLFOXIRI, fluorouracil, leucovorin, and irinotecan; OS, overall survival; PFS, progression-free survival.

*Log-rank test.
COUGAR-2

- Phase III trial of docetaxel vs BSC in met GE cancer post 5FU/platinum
- Docetaxel 75 mg/m² q 3 weeks up to 6 cycles (median 3 cycles – only 23% completed 6)
- OS 5.2 mos vs 3.6 HR 0.67 p =0.01
Randomized, Open-Label, Phase III Study Comparing Irinotecan With Paclitaxel in Patients With Advanced Gastric Cancer Without Severe Peritoneal Metastasis After Failure of Prior Combination Chemotherapy Using Fluoropyrimidine Plus Platinum: WJOG 4007 Trial

Shoichi Hiratsuka, Shinya Ueda, Hirofumi Yasui, Tomohiro Nishina, Masahiro Tsuda, Tack Hexo Tsunuma, Naoyuki Sugiura, Hidenori Shiokawara, Shinya Takanaga, Toshikazu Morikawa, Taito Ikari, Michirou Nogami, Kazumasa Fujita, Kensei Yamaguchi, Takashi Ura, Yusuo Hamamoto, Sazuki Morita, Banno Okamoto, Narisawa Boku, and Ichinoske Hyodo

Fig. 1. CONSORT diagram.
Chemotherapy options?

- **1st line:**
  - Platinum/5 FU based therapy – either cisplatin or oxaliplatin
  - Addition of anthracycline – depends on patient status - controversial
  - Consider irinotecan based therapy upfront for tolerability

Median OS 9.5 mos w/ Paclitaxel vs. 8.4 mos w/ irinotecan
Chemotherapy options

• 2\textsuperscript{nd} line
  – Irinotecan based
    • Or
  – Taxane based – weekly paclitaxel or q 3 weekly docetaxel
  – 5FU/platinum if irinotecan upfront
• 3\textsuperscript{rd} line
  – Whatever you haven’t used

Progress in Advanced Gastric Cancer:
OS with Combination Chemotherapy

3. Van Cutsem et al. JCO (2006); 4. Dank et al. ASCO 2005 (Abst 4003);
Biologics and Targeted Therapy
Fig. 1. Kaplan-Meier estimates of overall survival (A) and progression-free survival (B) in the intention-to-treat population. HR, hazard ratio.
Phase 3 RILOMET-1 Study

Key Eligibility

Inclusion
- Unresectable advanced or metastatic gastric or GESJ cancer
- ECOG PS 0-1
- Tumor/MET-positive by IHC (E 30-50, gain with tumor membrane staining)
- Evaluable disease by RECIST 1.1

Exclusion
- HER2-positive
- Previous systemic therapy for advanced disease
- 6 months from neoadjuvant chemotherapy
- Squamous cell histology
- LVEF < 50%

ClinicalTrials.gov Identifier: NCT01693072

Presented By David Cunningham at 2015 ASCO Annual Meeting

Study Design

Rilotumumab Cohort

Rilotumumab 15 mg/kg IV + EOX, 0.05W (n=106)

Placebo Cohort

Placebo + EOX, 0.05W (n=106)

Endpoints

Primary
- Overall survival

Secondary
- Progression-free survival
- Overall response rate
- Disease control rate
- AEs and immunogenicity
- Pharmacokinetics

Overall Survival

- More deaths in the rilotumumab arm, primarily due to disease progression

Presented By David Cunningham at 2015 ASCO Annual Meeting
**OS and MET Expression**

<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>Regorafenib  (n=204)</td>
<td>25%~&lt;45%</td>
<td>95</td>
<td>43</td>
<td>10.2</td>
<td>7.9~12.4</td>
</tr>
<tr>
<td></td>
<td>45%~&lt;80%</td>
<td>96</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>7.5~15.9</td>
</tr>
<tr>
<td>Placebo  (n=205)</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>29</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>

- Within the selected MET-positive population, higher MET expression (based on percentage of cells with 2+ MET staining) did not correlate with poorer prognosis or better outcome with regorafenib.

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**INTEGRATE: A randomized, phase II, double-blind, placebo-controlled study of regorafenib in refractory advanced oesophagogastric cancer (AOGC): A study by the Australasian Gastrointestinal Trials Group (AGITG)**

Final overall and subgroup results


ANZCTR 1261200239684

Presented By Nick Pavlakis at 2015 ASCO Annual Meeting
Study Schema

Nov 2012 - Feb 2014

Presented By Nick Pavlakis at 2015 ASCO Annual Meeting

Primary endpoint: Progression-Free Survival (PFS)

Median PFS: 2.6 mths (REG) v 0.9 mths (PBO)
HR: 0.40 (95% CI: 0.28 to 0.69)
Log-rank p <0.0001
Secondary endpoint: Overall Survival (OS)

- Median OS: 5.8 months (REG) vs 4.5 months (PBO)
- HR: 0.74 (95% CI: 0.51 to 1.08)
- Log-rank p=0.11

Number at risk:
- PBO: 50, 44, 37, 31, 27, 19, 14, 12, 10
- REG: 97, 93, 83, 67, 58, 48, 39, 34, 32

Presented By Nick Pavlakis at 2015 ASCO Annual Meeting

KEYNOTE-012: Gastric Cancer Cohort

Patients:
- Recurrent or metastatic adenocarcinoma of the stomach or GEJ
- ECOG PS 0-1
- PD-L1-positive tumor
- No active brain metastases

Pembrolizumab 10 mg/kg Q2W

Complete Response
- Discontinuation Permitted

Partial Response or Stable Disease
- Treat for 24 months or until progression or intolerable toxicity
- Discontinue

Confirmed Progressive Disease

Screening: 65 of 162 (40%) patients assessed for PD-L1 expression had PD-L1-positive tumors

Patients: 10 patients from Asia and 30 patients from the rest of the world

Treatment: 10 mg/kg Q2W

Response assessment: Performed every 12 weeks per RECIST v1.1

Presented By Yung-Jue Bang at 2015 ASCO Annual Meeting
Best Overall Response, RECIST v1.1

<table>
<thead>
<tr>
<th></th>
<th>Central Review N = 36</th>
<th>Investigator Review N = 39</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>22.2 (10.1-39.2)</td>
<td>33.3 (19.1-50.2)</td>
</tr>
</tbody>
</table>

Best overall response, n (%)

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Central Review</th>
<th>Investigator Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial</td>
<td>8 (22.2)</td>
<td>13 (33.3)</td>
</tr>
<tr>
<td>Stable</td>
<td>5 (13.9)</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td>Progressive</td>
<td>19 (52.8)</td>
<td>23 (59.0)</td>
</tr>
<tr>
<td>No assessment</td>
<td>1 (2.8)</td>
<td>0</td>
</tr>
<tr>
<td>Not determined</td>
<td>3 (8.3)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Patients with measurable disease per RECIST v1.1 by central review at baseline. **All responses were confirmed. ***Patient with centrally evaluable disease at baseline who discontinued therapy due to clinical progression before the first scan. ****Patients with centrally evaluable disease at baseline for whom best overall response could not be determined.

Analysis cut-off date: March 23, 2016.

Presented By Yung-Jue Bang at 2015 ASCO Annual Meeting

Kaplan-Meier Estimates of Survival

- 6-month PFS rate: 28%
- Median PFS: 1.9 months (95% CI, 1.8-3.5)

- 6-month OS rate: 66%
- Median OS: 11.4 months (95% CI, 5.7-NR)

Analysis cut-off date: March 23, 2016.

Presented By Yung-Jue Bang at 2015 ASCO Annual Meeting
Summary and Conclusions

- Durable efficacy in heavily pretreated, PD-L1–positive population
  - 22% ORR per RECIST v1.1 by central review
  - 40-week median duration of response
  - 11-month median OS
- Manageable safety profile, with no new events observed
- PD-L1 expression on both tumor and immune cells appears may be important to enrich the patient population
- Data support further study of pembrolizumab for advanced gastric cancer
  - KEYNOTE-059 (NCT02335411): phase 2 study of pembrolizumab monotherapy or in combination with chemotherapy
  - KEYNOTE-061 (NCT02370498): phase 3 study of pembrolizumab vs paclitaxel as second-line therapy

REGARD: Study Design

- Gastric or GEJ adenocarcinoma (metastatic or locally advanced and unresectable)
- Prior platinum and/or fluoropyrimidine
- ECOG PS 0-1
- No brain or CNS metastases
- Measurable or evaluable disease (defined by RECIST version 1.0)

Stratify
- Geographic region
- Weight loss (≥10% vs. <10%) over the prior 3 months
- Location of primary tumor (gastric vs. GEJ)

Randomize 2:1

N = 355

Every 2 weeks

Placebo

Ramucirumab 8 mg/kg + Best supportive care

Until progression

Study locations: Europe; North, South, and Central America; Asia, Africa, Australia/New Zealand

Presented By Yung-Jue Bang at 2015 ASCO Annual Meeting
REGARD: Overall Survival

**HR (95% CI) = 0.776 (0.603, 0.998)**  
Log-rank p-value (stratified) = .047

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ramucirumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients/events</td>
<td>117/99</td>
<td>238/179</td>
</tr>
<tr>
<td>Median OS, mos (95% CI)</td>
<td>3.8 (2.8, 4.7)</td>
<td>5.2 (4.4, 5.7)</td>
</tr>
<tr>
<td>6-month OS, %</td>
<td>32</td>
<td>42</td>
</tr>
<tr>
<td>12-month OS, %</td>
<td>12</td>
<td>18</td>
</tr>
</tbody>
</table>

**Placebo vs Ramucirumab**

**Number at Risk**

Placebo: 117  66  34  20  7  4  2  1  0  
Ramucirumab: 238  154  92  49  17  7  3  0  0

**Time Since Randomization, Months**

**Overall Survival, %**

**Fuchs et al. Lancet 2013;[Epub Ahead of print].**

**Rainbow: Study Design**

**1:1**

**Randomize**

- **Ramucirumab 8 mg/kg day 1&15**
  + **Paclitaxel 80 mg/m² day 1,8 &15**
  of a 28-day cycle
  N = 330

- **Placebo day 1&15**
  + **Paclitaxel 80 mg/m² day 1,8 &15**
  N = 335

**Treat until disease progression or intolerable toxicity**

**Survival and safety follow-up**

**Important inclusion criteria:**
- Metastatic or loc. adv. unresectable gastric or GEJ* adenocarcinoma
- Progression after 1st line platinum/fluoropyrimidine based chemotherapy

**Stratification factors:**
- Geographic region,
- Measurable vs non-measurable disease,
- Time to progression on 1st line therapy (< 6 mos vs. ≥ 6 mos)

* GEJ = gastroesophageal junction; gastric and GEJ will be summarized under the term GC
### RAINBOW: Overall Survival

**HR (95% CI) = 0.807 (0.678, 0.962)**  
Stratified log rank p-value = 0.0169

<table>
<thead>
<tr>
<th>Patients / Events</th>
<th>RAM + PTX</th>
<th>PBO + PTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients / Events</td>
<td>330 / 256</td>
<td>335 / 260</td>
</tr>
<tr>
<td>Median(mos) (95% CI)</td>
<td>9.63 (8.48, 10.81)</td>
<td>7.36 (6.31, 8.38)</td>
</tr>
<tr>
<td>6-month OS</td>
<td>72%</td>
<td>57%</td>
</tr>
<tr>
<td>12-month OS</td>
<td>40%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Δ mOS = 2.3 months

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### RAINBOW: Progression-free Survival & Response Rates

**HR (95% CI) = 0.635 (0.536, 0.752)**  
Stratified log rank p-value < 0.0001

<table>
<thead>
<tr>
<th>Patients / Events</th>
<th>RAM + PTX</th>
<th>PBO + PTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients / Events</td>
<td>330 / 279</td>
<td>335 / 296</td>
</tr>
<tr>
<td>Median(mos) (95% CI)</td>
<td>4.40 (4.24, 5.32)</td>
<td>2.86 (2.79, 3.02)</td>
</tr>
<tr>
<td>6-Month PFS</td>
<td>36%</td>
<td>17%</td>
</tr>
<tr>
<td>9-Month PFS</td>
<td>22%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Response Rate 28% 16%  
*p = 0.0001*

Disease Control Rate 80% 64%  
*p < 0.0001*
p-CODR

- The pCODR Expert Review Committee (pERC) recommends funding ramucirumab (Cyramza) in combination with paclitaxel, conditional on the cost-effectiveness being improved to an acceptable level.
- Funding should be for the treatment of patients with advanced or metastatic gastric cancer or gastro-esophageal junction (GEJ) adenocarcinoma with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and with disease progression following first-line chemotherapy.

- pERC does not recommend funding ramucirumab monotherapy for the treatment of patients with advanced or metastatic gastric cancer or GEJ adenocarcinoma with disease progression following first-line chemotherapy as there was considerable uncertainty in the net clinical benefit of ramucirumab monotherapy compared with usual care in the Canadian second-line setting.
- Although ramucirumab monotherapy offers another treatment option to patients, the modest survival benefit and uncertainty in the generalizability of the results led pERC to conclude that it partially aligns with patient values.
- The Committee also concluded that ramucirumab monotherapy was not cost-effective compared with placebo.
Take Home Points

• Metastatic
  – c-MET is negative – second negative study
  – Regorafenib – interesting? – warrants Phase III but needs to evaluate this in context Ramucirumab (will this be another 1.5 – 2 month benefit???)
  – Checkpoint inhibitors seem promising – staining may provide a biomarker

Now what?

• C-met – negative trials – maybe worse!
• Consider Ramucirumab with paclitaxel as a second line option (post first line 5FU/platinum) – is it reasonable post first line irinotecan??
• Immunotherapy looks promising
• Regorafenib – to enter possible Phase III
First stage analysis of irinotecan, capecitabine (Xeloda®), and oxaliplatin (IXO) as first-line treatment of HER2- metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma

Jennifer Spratlin, MD FRCPC
Grand Rounds
March 10, 2015
Dosing and Toxicity

• **Initial starting doses**
  - I: 160mg/m²
  - X: 950mg/m² BID
  - O: 100mg/m²

• 5 patients had dose limiting toxicity in the first two cycles

• 78% of patients required dose reductions (n=7/9 patients)

• 78% experienced grade 3/4 toxicity (n=7/9 patients)

• **Amendment doses**
  - I: 120mg/m²
  - X: 712.5mg/m² BID
  - O: 85mg/m²

• 1 patient had dose limiting toxicity in the first two cycles

• 50% of patients required dose reductions (n=8/16 patients)

• 37.5% experienced grade 3/4 toxicity (n=6/16 patients)

The overall response rate was 70.8% and disease control rate was 95.8% (17 partial responses, 6 stable, and 1 progressive disease as best response by RECIST criteria). Median time to progression was 8.3 months; median survival was 11.0 months.
New molecular classification

CIN
- Intestinal histology
- TP53 mutation
- RTK-RAS activation

EBV
- PK3CA mutation
- PD-L1/2 overexpression
- EBV-CIMP
- CDKN2A silencing
- Immune cell signaling

GS
- Diffuse histology
- CDH1, RHOA mutations
- CLDN18-ARHGAP fusion
- Cell adhesion

MSI
- Hypermutation
- Gastric-CIMP
- MMR1 silencing
- Mitotic pathways

Thank you!