Optimising anti-angiogenic strategies in gastric adenocarcinoma

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INTRODUCTION

Optimising anti-angiogenic strategies in gastric adenocarcinoma
Gastric adenocarcinoma

- Although its overall incidence is constantly decreasing, gastric adenocarcinoma remains the fourth leading cause of cancer death worldwide\(^1\)

- In patients with operable disease, surgery alone results in relatively poor long-term survival. In this situation, patients benefit from perioperative chemotherapy, adjuvant chemotherapy, or post-operative chemoradiation\(^2-5\)

4. GASTRIC Group. JAMA 2010;303:1729-37;
Treatment of HER-2 negative metastatic gastric adenocarcinoma in the first-line setting

- In patients with advanced disease, combination chemotherapy has proven a survival benefit over best supportive care alone and is the corner-stone of the treatment for patients with human epidermal growth factor receptor 2 (HER-2) negative disease.

- Although there is no international consensus regarding the optimal first-line chemotherapy regimen, a doublet with a platinum and fluoropyrimidine or a triplet regimen with the addition of docetaxel or epirubicin is frequently used.

- The median overall survival of HER-2 negative metastatic patients is between 9 months and 1 year.

Treatment of HER-2 positive metastatic gastric adenocarcinoma in the first-line setting

- For patients with HER-2 positive tumour, trastuzumab has become, in association with platinum and fluoropyrimidine doublet, the standard of care in the first-line metastatic setting, since the randomised phase III ToGA (Trastuzumab for Gastric Cancer) study.

- In this study, patients have a significantly increase of their median overall survival with trastuzumab: 13.8 months versus 11.1 months with chemotherapy alone (HR=0.74; [95%CI: 0.60- 0.91] (p=0.0046))

- Continuing trastuzumab beyond progression is still a non answered question

Bang YJ, Lancet 2010;376:687-97
Angiogenesis in cancer

- Angiogenesis is the formation of new blood vessels from pre-existing vessels and is an essential process in malignant tumour growth, progression and metastasising process.

- Vascular Endothelial Growth Factors (VEGF) and VEGF receptors (VEGFRs) are known as a the main part of the angiogenesis signaling pathways since the early 1990s.

There are 5 members of the VEGF family (VEGF-A, VEGF-B, VEGF-C, VEGF-D, and VEGF-E), and 2 placental growth factors (PIGF-1,-2)

There are 3 VEGFRs: VEGFR-1 and -2, mostly expressed in endothelial cells whereas VEGFR-3 has been found mostly associated with lymphangiogenesis

Angiogenesis in cancer

- The majority of anti-angiogenic treatment used in the clinic are based upon the inhibition of VEGF/VEGFR signalling

Vasudev NS, Reynolds AR. Angiogenesis 2014;17:471-94. This is an open access article distributed under the terms of the Creative Commons Attribution License
Angiogenesis in gastric cancer

- Neoplastic angiogenesis and lymphangiogenesis represent a critical process for tumour growth, invasion and metastatic spread
  - Altered or abnormal expression of tumour angiogenesis-related factors is associated with poor prognosis in several tumour types, including gastric cancer

Angiogenesis in gastric cancer

- Tumour angiogenesis has also been associated with response or resistance to chemotherapy in several clinical and preclinical models
  - Hypoxic conditions could impair tumour drug penetration thus limiting chemotherapy efficacy
  - VEGF polymorphisms may have predictive role in platinum-based chemotherapy sensitivity

Angiogenesis in gastric cancer
preclinical data

- In patients with gastric cancer, circulating VEGF levels are associated with increased tumour aggressiveness and reduced survival\(^1\),\(^2\)

- In animal models of gastric adenocarcinoma, VEGF/VEGFR inhibition reduced tumour growth and vascularity\(^3\)

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Angiogenesis in gastric cancer
clinical data

- Monoclonal antibodies, soluble receptors, and small-molecule tyrosine kinase inhibitors have been developed to inhibit tumour angiogenesis

- Several of these drugs have been tested in phase II studies in gastric cancer

- Three drugs, bevacizumab, ramucirumab and apatinib, have been evaluated in phase III trials
Optimising anti-angiogenic strategies in gastric adenocarcinoma

BEVACIZUMAB
Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor (VEGF)-A.

Encouraging results* were reported in combination with chemotherapy in first-line metastatic setting in phase II studies.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>N</th>
<th>ORR (%)</th>
<th>Median PFS Months (95%CI)</th>
<th>Median OS Months (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shah MA 2006</td>
<td>Irinotecan-cisplatin BEV</td>
<td>47</td>
<td>65</td>
<td>8.3 (5.5-9.9)</td>
<td>12.3 (11.3-17.2)</td>
</tr>
<tr>
<td>El-Rayes BF 2010</td>
<td>Docetaxel-Oxaliplatin BEV</td>
<td>38</td>
<td>42</td>
<td>6.6 (4.4-10.5)</td>
<td>11.1 (8.2-15.3)</td>
</tr>
<tr>
<td>Uronis HE 2013</td>
<td>Capecitabine-Oxaliplatin BEV</td>
<td>35</td>
<td>51.4</td>
<td>7.2 (5.4–8.5)</td>
<td>10.8 (8.7–14.5)</td>
</tr>
</tbody>
</table>

* Published results
Angiogenesis in gastric cancer bevacizumab

AVAGAST (Avastin for Advanced Gastric Cancer) study was the randomised phase III clinical trial evaluating the efficacy of bevacizumab in combination with chemotherapy.

- AVAGAST (Avastin for Advanced Gastric Cancer) study was the randomised phase III clinical trial evaluating the efficacy of bevacizumab in combination with chemotherapy.

Metastatic/Locally Advanced GC
N=774

Primary end point = overall survival (OS)

Bevacizumab + fluoropyrimidine-cisplatin (N=387)

Placebo + fluoropyrimidine-cisplatin (N=387)

Until disease progression

Angiogenesis in gastric cancer bevacizumab

### AVAGAST study: patients profile

<table>
<thead>
<tr>
<th>Geographic region</th>
<th>Fluoropyrimidine-cisplatin + bevacizumab (n=387)</th>
<th>Fluoropyrimidine-cisplatin + placebo (n=387)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia-Pacific</td>
<td>188 (49%)</td>
<td>188 (49%)</td>
</tr>
<tr>
<td>Europe</td>
<td>125 (32%)</td>
<td>124 (32%)</td>
</tr>
<tr>
<td>Pan America</td>
<td>74 (19%)</td>
<td>75 (19%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site of primary tumour</th>
<th>Fluoropyrimidine-cisplatin + bevacizumab (n=387)</th>
<th>Fluoropyrimidine-cisplatin + placebo (n=387)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>333 (86%)</td>
<td>338 (87%)</td>
</tr>
<tr>
<td>Gastro-oesophageal junction</td>
<td>54 (14%)</td>
<td>49 (13%)</td>
</tr>
</tbody>
</table>

Angiogenesis in gastric cancer
bevacizumab

The adjunction of bevacizumab showed no significant increase in overall survival: HR=0.87 (95% CI 0.73-1.03) p=0.1002
Median Overall Survival: 12.1 vs. 10.1 months

Angiogenesis in gastric cancer bevacizumab

The adjunction of bevacizumab significantly increased the progression-free survival: HR=0.80 (95%CI 0.68-0.93) p=0.0037; Median PFS: 6.7 vs. 5.3 months

Angiogenesis in gastric cancer bevacizumab

The adjunction of bevacizumab significantly increased the response rate

<table>
<thead>
<tr>
<th>Response</th>
<th>Bevacizumab</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>46%</td>
<td>37.4%</td>
<td>0.0315</td>
</tr>
<tr>
<td></td>
<td>40.3 to 51.7</td>
<td>31.9 to 43.1</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1.6%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>44.4%</td>
<td>36.4</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>29.9%</td>
<td>30.3%</td>
<td></td>
</tr>
</tbody>
</table>

Unadjusted analysis of efficacy (intention-to-treat population)

Angiogenesis in gastric cancer
bevacizumab

Adverse events

- The overall incidence of grade 3 to 5 adverse events was 76% in the bevacizumab group and 77% in the placebo group.

- **Diarrhea (D)** and **hand-foot syndrome (HFS)** incidences were increased in the bevacizumab arm (D: 8% vs. 4%) (HFS 6% vs. 3%).

- As expected, a higher incidence of **hypertension (HTN)** and **GI perforation** were noted in the bevacizumab group (g3 HTN 6% vs. 1%) (GI perforation 2% vs. 1%).

- Venous/Arterial thromboembolic events and bleeding were both similar in the 2 treatment arms.

Angiogenesis in gastric cancer bevacizumab

Possible regional variation in efficacy?

A greater benefit in South America, North America and Europe (vs. Asia)?

Angiogenesis in gastric cancer bevacizumab

Possible regional variation in efficacy?

- Differences in efficacy results between Asian and Non-Asian patients were not explained by significant difference in bevacizumab pharmacokinetics\(^1\)

- The phase III AVATAR study recently showed no improvement in OS or PFS in Chinese patients treated with bevacizumab plus capecitabine and cisplatin\(^2\)

Angiogenesis in gastric cancer
bevacizumab: Biomarkers study

- In AVAGAST, high baseline plasma levels of VEGF-A and low neuropilin-1 tumour expression (IHC) seemed to have both prognostic and predictive roles in non-Asian patients treated with bevacizumab.

- On the contrary, patients from Asia-Pacific had:
  - Lower baseline VEGF-A levels and those with high baseline VEGF-A levels did not demonstrate benefit from bevacizumab.
  - A lower Neuropilin-1 expression score (maybe confounded by the tissue acquisition).

Angiogenesis in gastric cancer bevacizumab in perioperative setting

- **ST03 (MAGIC-B)** was a multicentre, randomised, phase II/III study comparing perioperative ECX with or without bevacizumab (ECX-B)
  - 1063 patients were recruited in the phase III

- 200 eligible patients with histologically proven gastric or oesophago-gastric junction (OGJ) adenocarcinoma (Siewert type II or III), stage Ib-IV (T4N1-2M0) has been randomised in the phase II part of the trial. In the first analysis, wound-healing complications and tumour perforations were not increased by bevacizumab

- Final results showed no improvement in overall, disease-free or progression-free survival with bevacizumab and suggest an increased risk of post-operative anastomotic leak

Optimising anti-angiogenic strategies in gastric adenocarcinoma

RAMUCIRUMAB
Ramucirumab (IMC-1121B, LY3009806) is a fully humanised monoclonal antibody directed against the extracellular domain of VEGFR-2.

In a phase I study of 37 patients, 4 partial responses (11%) were observed, including one with previously treated gastric cancer. The safety profile was similar to that of bevacizumab, with serious adverse events including dose-related hypertension, venous thromboembolism and proteinuria.

Two phase III studies were designed in GC: REGARD and RAINBOW trials.

**REGARD** study was an international, randomised, double-blind, placebo-controlled phase 3 trial evaluating ramucirumab monotherapy in second-line setting.

**Metastatic/Locally Advanced GC/JOG Adenocarcinoma**

disease progression after first-line platinum-containing or fluoropyrimidine-containing chemotherapy

**N=355**

Primary end point = overall survival (OS)

Ramucirumab 8 mg/kg / 2 weeks

**N=238**

**R**

2:1

Until disease progression

Placebo

**N=117**

Angiogenesis in gastric cancer
ramucirumab

REGARD study: patients profile

<table>
<thead>
<tr>
<th></th>
<th>Ramucirumab (n=238)</th>
<th>Placebo (n=117)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race (by self report)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>181 (76%)</td>
<td>91 (78%)</td>
</tr>
<tr>
<td>Asian</td>
<td>39 (16%)</td>
<td>17 (15%)</td>
</tr>
<tr>
<td>Black</td>
<td>4 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Other</td>
<td>14 (6%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td><strong>Geographic region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America, Europe, Australia, New Zealand</td>
<td>165 (69%)</td>
<td>80 (68%)</td>
</tr>
<tr>
<td>Asia</td>
<td>18 (8%)</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>South/Central America, India, South-Africa, Middle East</td>
<td>55 (23%)</td>
<td>29 (25%)</td>
</tr>
<tr>
<td><strong>Site of primary tumour</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric</td>
<td>178 (75%)</td>
<td>87 (74%)</td>
</tr>
<tr>
<td>Gastro-oesophageal junction</td>
<td>60 (25%)</td>
<td>30 (26%)</td>
</tr>
</tbody>
</table>

## REGARD study: patients profile

<table>
<thead>
<tr>
<th>Feature</th>
<th>Ramucirumab (n=238)</th>
<th>Placebo (n=117)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histological subtype (Lauren classification)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinal</td>
<td>52 (22%)</td>
<td>35 (30%)</td>
</tr>
<tr>
<td>Diffuse</td>
<td>96 (40%)</td>
<td>44 (38%)</td>
</tr>
<tr>
<td>Unknown or not available</td>
<td>90 (38%)</td>
<td>38 (32%)</td>
</tr>
<tr>
<td><strong>Primary tumour present</strong></td>
<td>174 (73%)</td>
<td>86 (74%)</td>
</tr>
<tr>
<td><strong>Number of metastatic sites</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>163 (68%)</td>
<td>71 (61%)</td>
</tr>
<tr>
<td>≥3</td>
<td>75 (32%)</td>
<td>46 (39%)</td>
</tr>
<tr>
<td><strong>Peritoneal metastases</strong></td>
<td>64 (27%)</td>
<td>45 (38%)</td>
</tr>
</tbody>
</table>

Angiogenesis in gastric cancer
ramucirumab

Overall survival was significantly increased by ramucirumab
HR=0.776 95%CI [0.603-0.998]; p=0.047

Median overall survival:
Ramucirumab: 5.2 months (2.3-9.9)
Placebo: 3.8 months (1.7-7.1)

Angiogenesis in gastric cancer
ramucirumab

Progression-free survival was significantly increased by ramucirumab: HR=0.483 95%CI [0.376-0.620]; p<0.0001

Median progression-free survival:
Ramucirumab: 2.1 months (1.3-4.2)
Placebo: 1.3 months (1.1-2.1)

Angiogenesis in gastric cancer ramucirumab

More patients reported an improvement of their quality of life (6 weeks after treatment initiation)

Adverse events

■ Ramucirumab was associated with increased rates of hypertension (HTN) including grade 3 or more HTN: 8% in the ramucirumab arm versus 3% in the placebo arm

■ Bleeding, proteinuria, venous thrombotic events or gastrointestinal perforation were not increased by ramucirumab

■ Only arterial thrombotic events were slightly more common in the ramucirumab arm (4 events (2%) including 3 grade ≥3 events versus 0; p=0.55)
Angiogenesis in gastric cancer
ramucirumab: Discussion

- The survival benefit for ramucirumab versus placebo, although small\(^1\), is similar to that reported in the phase 3 trials comparing second-line cytotoxic chemotherapy with best supportive care (median 5.3 months vs. 3.8 months (HR 0.657)\(^2\) and 5.2 months vs. 3.6 months (HR 0.67)\(^3\)

- The survival benefit associated with ramucirumab was similar between Asian patients and the rest of the world (ROW) although relatively few Asian patients were enrolled

Angiogenesis in gastric cancer
ramucirumab + paclitaxel

- **RAINBOW** study was an international, randomised, double-blind, placebo-controlled phase 3 trial in second-line setting evaluating ramucirumab in combination with chemotherapy

**Primary end point** = overall survival (OS)

**Stratification Factors** = Geographic region, time to progression after first dose of first-line therapy and disease measurability

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**Metastatic/Locally advanced Gastric/GEJ Adenocarcinoma**

- Disease progression during or within 4 months of the last dose of first-line platinum and fluoropyrimidine doublet
- \( N = 665 \)

**Randomisation (R)**

1:1

- **Ramucirumab** 8 mg/kg D1, D15 + paclitaxel 80 mg/m² D1, 8, 15 (D1=D28) \( N = 330 \)

- **Placebo** D1, D15 + paclitaxel 80 mg/m² D1, 8, 15 (D1=D28) \( N = 335 \)

**Until disease progression**

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GEJ = gastroesophageal junction
Angiogenesis in gastric cancer
ramucirumab + paclitaxel

**RAINBOW** study: patients profile

<table>
<thead>
<tr>
<th>Ethnic Origin (by self report)</th>
<th>Ramucirumab plus paclitaxel (n=330)</th>
<th>Placebo plus paclitaxel (n=335)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>208 (63%)</td>
<td>199 (59%)</td>
</tr>
<tr>
<td>Asian</td>
<td>110 (33%)</td>
<td>121 (36%)</td>
</tr>
<tr>
<td>Black or other</td>
<td>12 (4%)</td>
<td>15 (4%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Geographic region</th>
<th>Ramucirumab plus paclitaxel (n=330)</th>
<th>Placebo plus paclitaxel (n=335)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. (Europe, Israel, Australia, USA)</td>
<td>198 (60%)</td>
<td>200 (60%)</td>
</tr>
<tr>
<td>2. (Argentina, Brazil, Chile, Mexico)</td>
<td>23 (7%)</td>
<td>21 (6%)</td>
</tr>
<tr>
<td>3. (Japan, South Korea, Hong Kong, Singapore, Taiwan)</td>
<td>109 (33%)</td>
<td>114 (34%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site of primary tumour</th>
<th>Ramucirumab plus paclitaxel (n=330)</th>
<th>Placebo plus paclitaxel (n=335)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>264 (80%)</td>
<td>264 (79%)</td>
</tr>
<tr>
<td>Gastroesophageal junction (GEJ)</td>
<td>66 (20%)</td>
<td>71 (21%)</td>
</tr>
</tbody>
</table>

Angiogenesis in gastric cancer
ramucirumab + paclitaxel

**RAINBOW study: patients profile**

<table>
<thead>
<tr>
<th></th>
<th>Ramucirumab plus paclitaxel (n=330)</th>
<th>Placebo plus paclitaxel (n=335)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histological subtype</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinal</td>
<td>145 (44%)</td>
<td>135 (40%)</td>
</tr>
<tr>
<td>Diffuse</td>
<td>115 (35%)</td>
<td>133 (40%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>21 (6%)</td>
<td>14 (4%)</td>
</tr>
<tr>
<td>Unknown or not available</td>
<td>49 (15%)</td>
<td>53 (16%)</td>
</tr>
<tr>
<td><strong>Primary tumour present</strong></td>
<td>209 (63%)</td>
<td>209 (62%)</td>
</tr>
<tr>
<td><strong>Number of metastatic sites</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>209 (63%)</td>
<td>232 (69%)</td>
</tr>
<tr>
<td>≥3</td>
<td>121 (37%)</td>
<td>103 (31%)</td>
</tr>
<tr>
<td><strong>Peritoneal metastases</strong></td>
<td>163 (49%)</td>
<td>152 (45%)</td>
</tr>
</tbody>
</table>

Angiogenesis in gastric cancer
ramucirumab + paclitaxel

Ramucirumab with paclitaxel significantly improved overall survival (OS) over paclitaxel + placebo: HR 0.807; p=0.017
Median OS 9.6 months versus 7.4 months

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Angiogenesis in gastric cancer
ramucirumab + paclitaxel

Ramucirumab with paclitaxel significantly improved progression-free survival over paclitaxel + placebo: HR 0.635; p<0.0001
Median PFS 4.4 months versus 2.9 months

Angiogenesis in gastric cancer ramucirumab + paclitaxel

The efficacy may be different according to geographic regions?

<table>
<thead>
<tr>
<th>Region</th>
<th>Median overall survival</th>
<th>Hazard ratio (95% CI)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regions 1 (n=398) and 2 (n=44)</td>
<td>8.5 months (7.4-9.8)</td>
<td>0.732</td>
<td>(0.591-0.907)</td>
</tr>
<tr>
<td>Region 3 (n=223)</td>
<td>12.1 months (10.0-13.3)</td>
<td>0.986</td>
<td>(0.727-1.337)</td>
</tr>
<tr>
<td>Median progression-free survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region 1 (n=398) and 2 (n=44)</td>
<td>4.2 months (3.9-4.9)</td>
<td>0.639</td>
<td>(0.518-0.788)</td>
</tr>
<tr>
<td>Region 3 (n=223)</td>
<td>5.5 months (4.2-5.7)</td>
<td>0.628</td>
<td>(0.473-0.834)</td>
</tr>
<tr>
<td>Proportion of patients achieving an objective response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region 1 (n=398) and 2 (n=44)</td>
<td>55 (25%)</td>
<td>2.087</td>
<td>(1.278-3.409)</td>
</tr>
<tr>
<td>Region 3 (n=223)</td>
<td>37 (34%)</td>
<td>2.235</td>
<td>(1.177-4.244)</td>
</tr>
</tbody>
</table>

Region 1 = Europe, Israel, Australia, USA
Region 2 = Argentina, Brazil, Chile, and Mexico
Region 3 = Japan, South Korea, Hong Kong, Singapore, and Taiwan

Adverse events

- The **incidence of grade 3-4 adverse events** was higher in the ramucirumab plus paclitaxel group:
  - Neutropenia (55%) (similar incidence of febrile neutropenia: 3% vs. 2%)
  - Neuropathy (46%)
  - Abdominal pain (36%)
  - Leucopenia (35%)
  - Hypertension (15%)
  - Fatigue (12%)
  - Gastrointestinal perforation (1.2%)

- **Treatment-related deaths** were comparable between the two arms

The preplanned subgroup analysis showed that Asian patients (region 3) have no overall survival benefit from ramucirumab (region 3: HR 0.986) whereas their median progression-free survival was increased compared with placebo plus paclitaxel (similarly to the entire population).

The higher use of post-progression therapy in Asia (69%) than in the non-Asian regions (38%) may explain these results.

A post-hoc analysis showed similar OS and PFS in Japanese vs. Western patients.

One phase II study in combination with FOLFOX (versus FOLFOX + placebo) with negative results:
- Progression-free survival: 6.4 vs. 6.7 months - HR 0.98, 95%CI [0.69-1.37], p=0.89
- Overall survival: 11.7 vs. 11.5 months (HR=1.08)

The sub-group analysis questioned about a potential benefit for gastric/GEJ but not for oesophageal adenocarcinomas?

The question remains unanswered due to the small size of the sub-groups

Yoon HH, et al. ASCO 2014, Abstr. 4004
A Phase III study with ramucirumab in combination with capecitabine and cisplatin in participants with stomach cancer (RAINFALL) is currently ongoing in first-line metastatic setting (NCT02314117)

https://clinicaltrials.gov
Angiogenesis in gastric cancer
ramucirumab / bevacizumab discussion

- GC is a heterogeneous disease

- Inherent differences exist in disease biology, genetic factors, histology that may influence patient and treatment outcome

- The management of gastric cancer patients differs between Asia and the rest of the world (ROW) and can also explain the differences in efficacy results
The absence of benefit from bevacizumab in the AVAGAST study may be due to an important part of Asian patients (49%).

A lesser proportion of Asian patients were included in the ramucirumab trials ( REGARD 16%, RAINBOW 33-36%).
Optimising anti-angiogenic strategies in gastric adenocarcinoma

APATINIB
Apatinib (YN968D1) is a small-molecule VEGFR-2 tyrosine kinase inhibitor. It could also inhibit Ret, c-kit and c-src.

A phase I clinical trial showed antitumour activity in Chinese patients with metastatic gastric cancer.

A randomised placebo-controlled phase II study showed an improvement in PFS and OS in heavily pretreated Chinese patients (failure after two or more chemotherapy regimens).

Multicentre, randomised, double-blind, placebo-controlled phase III trial in multi-treated patients

- Advanced GC
  - Previously failed at least 2 lines of chemotherapy
  - N=273

- Apatinib 850 mg (N=181)
  - Until disease progression
- Placebo (N=92)

Primary end point = overall survival (OS)
Stratification factor = Number of metastatic sites (≤2 or >2)

Apatinib induced a significant improvement of overall survival,
- Median overall survival: 6.5 vs. 4.7 months, HR=0.709 95%CI [0.537-0.937] p=0.0149

A significant improvement of progression-free survival
- Median progression-free survival: 2.6 vs. 1.8 months, HR 0.444 95%CI [0.331-0.595] p<0.0001

A significant increase in disease control rate
- Disease control rate 31.82% vs. 10.99% (p=0.002)
Adverse events

- The incidence of adverse events was higher in the apatinib group:
  - All adverse events: 98.30% in the apatinib arm vs. 90.11% in the placebo arm (p=0.0038)
  - Grade 1-2 events: 88.07% vs. 67.03% (p=0.0001)
  - Grade 3-4 events: 60.23% vs. 41.76% (p=0.0045)

- Similar rate of serious adverse events: 15.34% vs. 16.48% (p=0.8598)

# Angiogenesis in gastric cancer: apatinib

## Grade 3/4 adverse events (incidence ≥5%)

<table>
<thead>
<tr>
<th></th>
<th>Apatinib N=176</th>
<th>Placebo N=91</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand-Foot syndrome</td>
<td>8.52%</td>
<td>0.00%</td>
<td>0.0032</td>
</tr>
<tr>
<td>Elevation of transaminases</td>
<td>7.95%</td>
<td>4.40%</td>
<td>0.3155</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>7.39%</td>
<td>6.59%</td>
<td>1.0000</td>
</tr>
<tr>
<td>Hypochromia</td>
<td>6.25%</td>
<td>4.40%</td>
<td>0.7799</td>
</tr>
<tr>
<td>Elevation of GGT</td>
<td>6.25%</td>
<td>6.59%</td>
<td>1.0000</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5.68%</td>
<td>1.10%</td>
<td>0.1045</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>5.11%</td>
<td>2.2%</td>
<td>0.3417</td>
</tr>
</tbody>
</table>

Angiogenesis in gastric cancer apatinib: Conclusion

- The data on apatinib in Chinese patients are highly significant and call for a confirmation in Caucasian patients.

- Apatinib is under evaluation in several situations in GC:
  - Maintenance therapy after first line treatment in locally advanced or metastatic gastric cancer (NCT02537171 and NCT02509806)
  - Compared to docetaxel treatment in patients with advanced gastric cancer after one prior chemotherapy regimen (NCT02409199)
  - In combination with S-1 as first-line treatment in patients with advanced gastric cancer (NCT02525237)
  - In combination with S1 and paclitaxel chemotherapy for unresectable untreated gastric cancer (NCT02529878)
CONCLUSION

Optimising anti-angiogenic strategies in gastric adenocarcinoma
Conclusion

- Angiogenesis plays a major role in gastric cancer development and progression

- Clinical data, despite some contradictory results, suggest that the inhibition of angiogenic signaling pathways has an important therapeutic potential

- Based on the positive results of the REGARD and RAINBOW trials, ramucirumab is the first anti-angiogenic treatment having FDA and EMA approval in advanced GC

- Ramucirumab is indicated as second line treatment alone or in combination with paclitaxel, in patients with advanced or metastatic gastric or oesophagogastric junction cancers who progressed on fluoropyrimidine-or platinum-containing first-line chemotherapy
Apatinib has been approved by the China Food and Drug Administration and will be certainly evaluated in Western countries. Its results are exciting.

Other antiangiogenic treatments (Ziv-Aflibercept, pazopanib, dovitinib…) are currently evaluated in phase II studies and may represent new tools in the future management of GC.
Thank you!