BIOLOGICAL TARGETED AGENTS
(INCLUDING HER2, EGFR, ANGIogenesis)

Dr Elizabeth Smyth
Royal Marsden Hospital

ESMO GI Cancer Preceptorship Singapore 2017
DISCLOSURES

Honoraria for advisory role
Five Prime Therapeutics, Servier, Bristol-Meyer Squibb, Gritstone Oncology
HER2, EGFR and VEGF signalling are dysregulated in 57% of TGCA gastroesophageal dataset

Dysregulation is more frequently due to amplification than mutation.
Amplifications most commonly occur in the chromosomally unstable (CIN) subtype. Rarely, amplifications also occur in GS, MSI, and EBV subtypes.
TARGETING HER2 IN GASTRIC CANCER
HER2 POSITIVE GASTRIC CANCER
ESMO Guidelines

TARGETING HER2 IN GASTRIC CANCER

TOGA trial

TOGA Trial

Treatment naïve advanced HER2 positive* gastric cancer

Cisplatin-5FU/X (n=296)

Cisplatin-5FU/X Trastuzumab (n=298)

Primary endpoint OS

Addition of trastuzumab to CF/X ↑ response rate, PFS and overall survival

TARGETING HER2 IN GASTRIC CANCER

TOGA trial

Trastuzumab is most effective in IHC 3+ or IHC 2+ FISH positive patients

TARGETING HER2 IN GASTRIC CANCER

Alternative chemotherapy regimens – oxaliplatin + trastuzumab

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Chemotherapy partner</th>
<th>ORR</th>
<th>mPFS</th>
<th>mOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soularue et al*</td>
<td>34</td>
<td>FOLFOX/XELOX</td>
<td>41%</td>
<td>9m</td>
<td>17.3m</td>
</tr>
<tr>
<td>Ryu et al</td>
<td>55</td>
<td>XELOX</td>
<td>67%</td>
<td>9.8m</td>
<td>21.0m</td>
</tr>
<tr>
<td>Gong et al</td>
<td>55</td>
<td>XELOX</td>
<td>68%</td>
<td>9.2m</td>
<td>19.5m</td>
</tr>
</tbody>
</table>

*retrospective

Outcomes appear similar to cisplatin and 5FU in TOGA

Caveat: Phase II, uncontrolled data

NCCN Gastric Cancer Guidelines 2017
Trastuzumab + cisplatin/5FU – Category 1
Trastuzumab + other chemotherapy – Category 2B

ORR, objective response rate
mPFS, median progression free survival
mOS, median overall survival

Soularue et al, Bull Cancer. 2015 Apr;102(4):324-31..
Gong et al, BMC Cancer. 2016 Feb 8;16:68.
TARGETING HER2 IN GASTRIC CANCER
Alternative chemotherapy regimens – cisplatin + S-1

HERBIS-1

S-1 80-120 mg D1-14
Cisplatin 60 mg² D1 q21D
+ Trastuzumab
n=55

Median OS and PFS were 16.0 months and 7.8 months

ORR 68%

Treatment naïve advanced HER2 positive* gastric cancer

*IHC 3+ or FISH positive

**TARGETING HER2 IN GASTRIC CANCER**

Alternative chemotherapy regimens – platinum free

**JACCRO GC-06**

- Treatment naïve advanced HER2 positive* gastric cancer
- Age ≥65y
- S-1 80-120 mg D1-14 q21D + Trastuzumab n=51

*IHC 3+ or FISH positive

- Median OS and PFS were 15.8 months and 5.1 months

ORR 40.8%

Kimura et al, Gastric Cancer. 2017 Sep 21.
PERTUZUMAB & TRASTUZUMAB IN HER2+VE GASTRIC CANCER

JACOB trial

International multicentre trial
Primary endpoint = OS

HER2 positive treatment naïve
GEJ/ GC

CF/X + Trastuzumab
(n=388)

CF/X + Trastuzumab + Pertuzumab
(n=392)

Objective response rate (ORR) in evaluable patients

<table>
<thead>
<tr>
<th></th>
<th>CF/X + T</th>
<th>CF/X + T + P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>56.7</td>
<td>48.3</td>
</tr>
<tr>
<td>Duration of ORR (m)</td>
<td>10.2</td>
<td>8.4</td>
</tr>
</tbody>
</table>

Progression free survival

<table>
<thead>
<tr>
<th></th>
<th>CF/X + T</th>
<th>CF/X + T + P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (months)</td>
<td>7.0</td>
<td>8.5</td>
</tr>
<tr>
<td>HR</td>
<td>0.73 (95%CI 0.62 - 0.86)</td>
<td></td>
</tr>
</tbody>
</table>

CF/X, cisplatin, 5-fluorouracil or capecitabine

Tabernero et al, ESMO 2017
PERTUZUMAB & TRASTUZUMAB IN HER2+VE GASTRIC CANCER

JACOB trial

International multicentre trial
Primary endpoint = OS

HER2 positive treatment naïve
GEJ/ GC

CF/X + Trastuzumab (n=388)

CF/X + Trastuzumab + Pertuzumab (n=392)

Despite 3.3 month absolute benefit in OS, no statistically significant benefit in OS for addition of pertuzumab

Tabernero et al, ESMO 2017
SECOND LINE ANTI-HER2 THERAPY IN GASTRIC CANCER

GATSBY TRIAL

**Objective response rate (ORR) in evaluable patients**

<table>
<thead>
<tr>
<th></th>
<th>Taxane</th>
<th>TDM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>19.6</td>
<td>20.6</td>
</tr>
<tr>
<td>Duration of response</td>
<td>3.7m</td>
<td>4.3m</td>
</tr>
</tbody>
</table>

**Progression free survival**

<table>
<thead>
<tr>
<th></th>
<th>Taxane</th>
<th>TDM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (months)</td>
<td>2.9</td>
<td>2.7</td>
</tr>
<tr>
<td>HR 1.13 (0.89–1.43), p=0.31 (two-sided)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SECOND LINE ANTI-HER2 THERAPY IN GASTRIC CANCER

GATSBY TRIAL

ANTI-HER2 THERAPY IN GASTRIC CANCER

WHY?

Lorenzen et al, Eur J Cancer 2015 Mar;51(5):569-76
Satoh T et al, J Clin Oncol 2014; 32:2039-2049
HER2 HETEROGENEITY IN GASTRIC CANCER

HER2 POSITIVE GASTRIC CANCER
Site, subtype and heterogeneity

TOGA HER2 positivity by site and histology

<table>
<thead>
<tr>
<th>Site of tumour</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>451/2112</td>
<td>21%</td>
</tr>
<tr>
<td>GEJ</td>
<td>65/202</td>
<td>32%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lauren subtype</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse</td>
<td>68/1108</td>
<td>6%</td>
</tr>
<tr>
<td>Intestinal</td>
<td>606/1904</td>
<td>32%</td>
</tr>
</tbody>
</table>

TOGA HER2 heterogeneity by IHC

- Heterogeneity = ≤ 30% staining
  - IHC1+ 86%
  - IHC2+ 55%
  - IHC3+ 30%

TOGA HER2 % of positive cells in IHC3+ patients

- % cells
  - <10% 3%
  - 10-30% 27%
  - 31-79% 31%
  - ≥80% 39%

Van Cutsem et al, Gastric Cancer (2015) 18:476–484
OPTIMAL CUT OFF FOR HER2 IN GASTRIC CANCER

Two studies identified HER2/CEP17 ratio of ~4.5 as optimal for predicting benefit from trastuzumab therapy.

Ock et al, Clin Cancer Res. 2015 Jun 1;21(11):2520-9
OPTIMAL CUT OFF FOR HER2 IN GASTRIC CANCER

In Korean study, gene copy was only important for patients who were HER2 IHC 2+.

Retrospective series

• 454 primary gastric tumours
  • 5 biopsies from each tumour made into tissue microarrays
  • Microarray HER2 status compared with slide from whole resection specimen
  • 24% false negative rate in TMA

• Similar number of patients could be missed on biopsy!

Prospective validation of multiple biopsies

• GastHER1 study
  • Repeat biopsy of HER2 negative tumour
  • ↑ HER2 positive rate by 8.7% (95% CI 4.6-12.8%)

• Biopsy of metastatic site when primary HER2↑ positive rate by 5.7% (95% CI4.6-12.8%)


CHALLENGES ASSOCIATED WITH HER2 HETEROGENEITY

Sampling error – retrospective and prospective studies
CHALLENGES IN HER2 POSITIVE GASTRIC CANCER

Dynamic changes in HER2 expression

HER status changes post trastuzumab therapy

22 pairs pre and post chemotherapy HER 3+ or HER 2+ FISH positive plus trastuzumab biopsies.

7/22 (32%) HER2 negative following treatment. More common in IHC2+ vs IHC3+

Non-HER2 biomarkers become important when HER2 changes

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Janjigian et al, ESMO 2016
TRASTUZUMAB/PERTUZUMAB IN HER2 POSITIVE GC
Pharmacokinetics differ from breast cancer

Steady-state exposure of trastuzumab is lower in GC than with same dose in MBC. Patients in lowest quartile had worse survival than upper three quartiles

Patients with lowest Cmin had the highest progression rate and worse overall survival.

↓ Albumin and ↑ weight associated with higher clearance

A phase II dose finding study (JOSHUA) preceded JACOB to optimize pertuzumab dose in GC (twice that of MBC)

Comparison of dosing regimens on day 43 trough levels of pertuzumab in JOSHUA

Yang et al, J Clin Pharmacol 53: 160–166
PERIOPERATIVE CHEMO + ANTI-HER2 IN GASTRIC CANCER

Ongoing trials

**INNOVATION EORTC 1203**
- Chemotherapy
- Chemotherapy + trastuzumab
- Chemotherapy plus pertuzumab + trastuzumab

**PETRARCHA (FLOT6)**
- FLOT ± trastuzumab/pertuzumab

**RTOG 1010**
- Carboplatin/paclitaxel + RT
  - + trastuzumab in GEJ

**TRIGGER (JCOG 1301)**
- Cisplatin+S1+Trastuzumab
  - in node positive GC
TARGETING EGFR IN GASTRIC CANCER
TARGETING EGFR IN GASTRIC CANCER
Dysregulation and co-amplification in oesophago-gastric TCGA

- EGFR: 10%
- ERBB2: 28%
- FGFR2: 5%
- MET: 7%
- KRAS: 15%

Genetic Alteration:
- Amplification
- Deep Deletion
- Inframe Mutation (putative driver)
- Missense Mutation (putative driver)
- Missense Mutation (putative passenger)

http://www.cbioportal.org
TARGETING EGFR IN GASTRIC CANCER

Dysregulation and co-amplification in oesophago-gastric TCGA

EGFR amplification is negatively prognostic


EGFR amplified GC PDX models are addicted to EGFR signalling.
EGFR IN GASTRIC CANCER
Cetuximab plus chemotherapy

EXPAND Trial

Cisplatin-X
N=449

Treatment naïve advanced GC/GEJ

Cetuximab
N=455

Primary endpoint PFS

Addition of cetuximab to CX did not increase response rate, PFS or overall survival

EGFR IN GASTRIC CANCER
Cetuximab plus chemotherapy

Suggestion that PFS may be prolonged in cetuximab treated patients with higher EGFR IHC score

EGFR IN GASTRIC CANCER
Panitumumab plus chemotherapy

REAL3 Trial

- Treatment naïve advanced GC/GEJ
- EOX N=275
- EOX Panitumumab N=278

Primary endpoint OS

Addition of panitumumab to EOX did not increase ORR and led to inferior PFS and OS

EOX, epirubicin, oxaliplatin and capecitabine


NB: lower dose of oxaliplatin and capecitabine in EOX-P arm
EGFR IN OESOPHAGEAL CANCER

Gefitinib

COG Trial

Previously treated oesophageal cancer
Adeno and SCC

Gefitinib 500mg od
N=224

Placebo
N=225

No benefit to gefitinib in progression free or overall survival in ITT population

EGFR IN OESOPHAGEAL CANCER

Gefitinib: COG trial biomarker analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Events/No.</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>317/340</td>
<td>0.88 (0.70 to 1.10)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR FISH status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FISH negative</td>
<td>212/233</td>
<td>0.90 (0.69 to 1.18)</td>
</tr>
<tr>
<td>FISH positive</td>
<td>57/59</td>
<td>0.59 (0.35 to 1.00)</td>
</tr>
<tr>
<td>Classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FISH negative</td>
<td>212/233</td>
<td>0.90 (0.69 to 1.18)</td>
</tr>
<tr>
<td>Polysomy</td>
<td>36/38</td>
<td>0.66 (0.34 to 1.30)</td>
</tr>
<tr>
<td>Amplified</td>
<td>21/21</td>
<td>0.21 (0.07 to 0.64)</td>
</tr>
</tbody>
</table>

Biomarker analysis: FISH for EGFR polysomy or amplification

OS in EGFR amplified patients

TARGETING ANGIOGENESIS IN GASTRIC CANCER
ANGIOGENESIS DYSREGULATION IN GC
Oesophagogastric TCGA dataset

Effect of VEGF expression on disease specific survival in resected GC

http://www.cbioportal.org
TARGETING ANGIOGENESIS IN GASTRIC CANCER

- Endothelial cell

- Dil4 notch

- ziv-aflibercept

- Bevacizumab

- PIGF VEGFB

- VEGFA

- Ramucirumab

- VEGFC VEGFD

- Ang1/ Ang2

- PDGF

- FGF

- NP1/ NP2

- VEGFR1

- VEGFR2

- VEGFR3

- Integrins

- Tie1/ Tie2

- PDGFR

- FGFR

- HSC survival
- Monocyte chemotaxis
- Inhibition of DC maturation

- Regorafenib
- Axitinib
- Pazopanib

- Lymphangiogenesis

Endothelial cell

Despite statistically significant improvements in ORR and PFS, no significant benefit in OS was demonstrated for bevacizumab treated patients.

BEVACIZUMAB IN GASTRIC CANCER: AVAGAST

Regional differences in outcome

Poor PS, liver mets, and larger tumours were most frequent in E Europe/South America >> Japan.

In chemotherapy treated patients subsequent chemotherapy after disease progression was used in E Europe/S America (14%); USA/W Europe (37%); Korea/other Asia (61%); and Japan (77%).

HR for OS vs USA/WEurope were 1.47 E. Europe/South America, 0.91 for Korea/other Asia, and 0.87 for Japan.

BEVACIZUMAB IN GASTRIC CANCER: AVATAR
CX vs CX-B in Chinese gastric cancer patients

Cis-Cape
N=100

Cis-Cape Bevacizumab
N=102

Primary endpoint OS

Median OS CX 11.4m vs 10.6m CX-B
HR 1.11 (95% CI, 0.79–1.56); P = 0.56

Cis= cisplatin, Cape=Capecitabine

BEVACIZUMAB IN OPERABLE GC/GEJ
ST03 Trial

Primary endpoint OS

Treatment naïve operable GC/GEJ

ECX N=530

ECX+Bev N=533

3 y OS ECX 50.3% vs 48.1m ECX-B
HR 1·09, 95% CI 0·91–1·29; log-rank p=0·36

Increased rate of anastomotic leaks in bevacizumab treated patients with oesophagogastrectomy

ECX= epirubicin, cisplatin and capecitabine

VEGFR2 INHIBITION IN GASTRIC CANCER: RAMUCIRUMAB

REGARD Trial

2nd line advanced GC/GEJ post platinum/5FU chemotherapy

Ramucirumab
N=238

Placebo
N=117

Primary endpoint OS

Median OS 5.2m vs 3.8m ram vs placebo
HR 0.776, 95% CI 0.603-0.998; p=0.047
ORR 4% ramucirumab

RAMUCIRUMAB IN GASTRIC CANCER
RAINBOW Trial

2\textsuperscript{nd} line advanced GC/GEJ post platinum/5FU chemotherapy

Paclitaxel plus ramucirumab
N=330

Paclitaxel plus placebo
N=335

Primary endpoint OS

Ramucirumab 8 mg/kg D1, D15 Q4W
Paclitaxel 80mg/m\textsuperscript{2} D1, D8, D15 Q4W

Median OS 9.6m vs 7.4m, HR 0.807 [95% CI 0.678-0.962]; p=0.017
ORR 28% vs 14%

RAMUCIRUMAB IN GASTRIC CANCER: RAINBOW TRIAL

Regional differences in outcome

RAMUCIRUMAB IN GASTRIC CANCER: RAINBOW TRIAL

Regional differences in outcome

Ramucirumab improved radiological response rates in Japanese and Western populations

Response rates to paclitaxel and paclitaxel ramucirumab are higher in Japanese patients

RAMUCIRUMAB IN GASTRIC CANCER: RAINBOW TRIAL
Regional differences in outcome: exploratory analysis

Patients without post discontinuation treatment have shorter survival in both populations, and clear benefit from ramucirumab

Patients with post discontinuation treatment have longer survival in both populations but magnitude of benefit from ramucirumab is smaller

# Toxicty of Antiangiogenic Therapy in Gastric Cancer

Grade 3 or greater toxicity in clinical trials

<table>
<thead>
<tr>
<th></th>
<th>AVAGAST</th>
<th>FOLFOX</th>
<th>RAINBOW</th>
<th>REGARD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>36%</td>
<td>37%</td>
<td>41%</td>
<td>18%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>5%</td>
<td>4%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6%</td>
<td>3%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>6%</td>
<td>9%</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>7%</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>6%</td>
<td>9%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8%</td>
<td>4%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>8%</td>
<td>11%</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Dehydration</td>
<td>9%</td>
<td>1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicties of special interest</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>6%</td>
<td>9%</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Arterial thromboembolism</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6%</td>
<td>&lt;1%</td>
<td>16%</td>
<td>4%</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>2%</td>
<td>2%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>GI perforation</td>
<td>2%</td>
<td>&lt;1%</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Note: All percentages rounded to nearest whole number.*

*Abbreviations: CX, cisplatin/capecitabine; FOLFOX, 5-fluorouracil/leucovorin/oxaliplatin; GI, gastrointestinal.*

RAMUCIRUMAB

Quality of life analysis in RAINBOW: QLQ-C30

RAMUCIRUMAB

Quality of life analysis in RAINBOW: QLQ-C30

TdD ≥PS2

TdD ≥1 PS value

## RAMUCIRUMAB IN GASTRIC CANCER

Multivariate analysis of factors associated with overall survival in REGARD and RAINBOW

<table>
<thead>
<tr>
<th>Prognostic factors of poor survival</th>
<th>HR (99% CI for mortality)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of a primary tumor</td>
<td>1.31 (1.05–1.62)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Poor/unknown tumor differentiation</td>
<td>1.33 (1.08–1.64)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Time to progression since prior therapy &lt;6 mo</td>
<td>1.35 (1.10–1.66)</td>
<td>0.0002</td>
</tr>
<tr>
<td>ECOG PS 1</td>
<td>1.39 (1.12–1.73)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Presence of peritoneal metastases</td>
<td>1.49 (1.22–1.83)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>High ALP level</td>
<td>1.28 (1.03–1.60)</td>
<td>0.0030</td>
</tr>
<tr>
<td>Low lymphocyte level</td>
<td>1.31 (1.05–1.63)</td>
<td>0.0015</td>
</tr>
<tr>
<td>High LDH level</td>
<td>1.31 (1.05–1.63)</td>
<td>0.0019</td>
</tr>
<tr>
<td>Low albumin level</td>
<td>1.33 (1.07–1.65)</td>
<td>0.0006</td>
</tr>
<tr>
<td>High AST level</td>
<td>1.37 (1.06–1.76)</td>
<td>0.0014</td>
</tr>
<tr>
<td>High neutrophil level</td>
<td>1.52 (1.17–1.99)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low sodium level</td>
<td>2.04 (1.54–2.71)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Prognostic index (No. of patients in each group=953)**

<table>
<thead>
<tr>
<th>Index</th>
<th>Score</th>
<th>Total No. of included patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0–2</td>
<td>107 (11.2)</td>
</tr>
<tr>
<td>Medium</td>
<td>3–4</td>
<td>322 (33.8)</td>
</tr>
<tr>
<td>Moderate</td>
<td>5–6</td>
<td>310 (32.5)</td>
</tr>
<tr>
<td>High</td>
<td>7–13</td>
<td>214 (22.5)</td>
</tr>
</tbody>
</table>

OS = overall survival; HR = hazard ratio; CI = confidence interval; ECOG = Eastern Cooperative performance status; ALP = alkaline phosphatase; LDH = lactate dehydrogenase; AST = aspartate transaminase.

Fuchs et al, J Gastric Cancer. 2017 Jun;17(2):132-144.
RAMUCIRUMAB IN GASTRIC CANCER
Multivariate analysis of factors associated with overall survival in REGARD and RAINBOW

Prognostic index (No. of patients in each group=953)

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Fuchs et al, J Gastric Cancer. 2017 Jun;17(2):132-144.
### RAMUCIRUMAB IN GASTRIC CANCER

Age and outcome

<table>
<thead>
<tr>
<th></th>
<th>REGARD HR (95% CI)</th>
<th>RAINBOW HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤45 years</td>
<td>0.59 (0.27-1.26)</td>
<td>0.56 (0.33-0.93)</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>0.80 (0.59-1.10)</td>
<td>0.78 (0.63-0.97)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>0.72 (0.48-1.08)</td>
<td>0.88 (0.66-1.18)</td>
</tr>
<tr>
<td>≥70 years</td>
<td>0.73 (0.44-1.23)</td>
<td>0.88 (0.60-1.28)</td>
</tr>
<tr>
<td>≥75 years</td>
<td>0.59 (0.25-1.37)</td>
<td>0.97 (0.47-2.01)</td>
</tr>
</tbody>
</table>

Muro et al, J Gastroenterol Hepatol. 2017 Sep 29..
**RAMUCIRUMAB IN GASTRIC CANCER: REGARD TRIAL**

**Biomarker analysis**

Non-significant trend for worse OS in high VEGFR2 expressing patients in placebo arm

Suggestion of OS benefit in high and low VEGFR expressing patients

Low levels of 6 biomarkers were prognostic in ramucirumab and placebo treated patients

No VEGF pathway biomarker or other maker had a predictive relationship with ramucirumab efficacy

Van Cutsem et al, ESMO 2016.
RAMUCIRUMAB EXPOSURE RESPONSE AND OS
Increased exposure associated with improved OS

RAINBOW

RAMUCIRUMAB EXPOSURE RESPONSE AND OS

Increased exposure associated with improved OS and increased toxicity

RAMUCIRUMAB FIRST LINE IN GASTRIC CANCER

Ramucirumab-FOLFOX

Treatment naïve advanced GC/GEJ post

FOLFOX
N=84

FOLFOX
ramucirumab
N=84

Primary endpoint PFS

Stopping treatment for reasons other than PD more common in the ramucirumab versus placebo arm (48% versus 16%)

PFS 6.4 vs 6.7m, HR 0.98 (95% CI 0.69–1.37)

FOLFOX, oxaliplatin; leucovorin plus 5-fluororacil

RAMUCIRUMAB FIRST LINE IN GASTRIC CANCER

Suggestion of differential benefit according to tumour location

1ST LINE RAMUCIRUMAB IN GASTRIC CANCER
RAINFALL trial NCT02314117

Randomized, double-blind phase III trial

Pts with metastatic gastric/GEJ cancer with no prior first-line therapy (N = 616, planned)

Ramucirumab 8 mg/kg IV Days 1, 8
Capecitabine* 1000 mg/m² PO Days 1-14
Cisplatin 80 mg/m² IV Day 1

Placebo IV Days 1, 8
Capecitabine* 1000 mg/m² PO Days 1-14
Cisplatin 80 mg/m² IV Day 1

*Pts unable to take capecitabine receive 5-FU 800 mg/m²/day Days 1-5.

21-day cycles

Primary endpoint: PFS
Secondary endpoints: OS, ORR, DCR, TTP, DoR, QoL

Primary endpoint is met
OS data is awaited
RAMUCIRUMAB FIRST LINE IN GASTRIC CANCER
RAINSTORM Trial NCT 02539225

**Screen**

**Patients**
- ≥20 years
- Metastatic gastric or GEJ adenocarcinoma
- No prior first-line systemic therapy
- Not HER2 positive

**Stratification**
- Geographic region (Japan / Korea)
- ECOG PS (0 / 1)
- Disease measurability (measureable / nonmeasurable)

**Part A (first line)**
- **Ramucirumab** IV (Days 1 and 8) + **S-1** by mouth (Days 1-14) and **oxaliplatin** IV (Day 1) of each 21-day cycle

**Part B (second line)**
- **Ramucirumab** IV (Days 1 and 15) + **paclitaxel** IV (Days 1, 8, and 15) of each 28-day cycle

**Pretreatment period of Part B**
- **Placebo** IV (Days 1 and 8) + **S-1** by mouth (Days 1-14) and **oxaliplatin** IV (Day 1) of each 21-day cycle
TARGETING ANGIOGENESIS IN GASTRIC CANCER
APATINIB (anti-VEGFR2 tyrosine kinase inhibitor)

Apatinib 850mg od
N=176

Placebo
N=91

3rd line +
GC/GEJ
China only

12.5% patients discontinued for toxicity
21% had dose modification

Ongoing international confirmatory study
ANGEL NCT03042611

Median OS 6.5m vs. 4.7m
HR 0.709 (95% CI, 0.537 – 0.937); P = .0149

Li et al, J Clin Oncol. 2016 May 1;34(13):1448-54.
TARGETING ANGIOGENESIS IN GASTRIC CANCER

Regorafenib (multitargeted tyrosine kinase inhibitor)

Pts with locally recurrent or metastatic gastric/GEJ (N = 147)

Regorafenib
160 mg PO Days 1-21 (n = 97)

Placebo
PO Days 1-21 (n = 50)

Regional HR for PFS
Australia, NZ and Canada 0.61 (95% CI 0.39-0.97)
South Korea 0.12 (95% CI 0.06-0.27)

Global phase III randomised INTEGRATE III NCT02773524

Placebo
Regorafenib

(Median PFS 2.6 vs 0.9 ms)

(HR 0.40; 95% CI: 0.28-0.59; P < .001)

COMBINATION ANTI-ANGIOGENIC AND IMMUNOTHERAPY

Ramucirumab plus pembrolizumab

Chau et al, ASCO 2017, abstract 4064
HER2 AND ANTIANGIOGENICS IN GASTRIC CANCER

Summary

HER2 directed therapy in advanced gastric cancer
- Positive clinical trial in 1st line for trastuzumab plus chemotherapy only (TOGA)
- No benefit to addition of pertuzumab to trastuzumab (JACOB)
- No positive trial for lapatinib (LOGIC, TyTAN)
- No positive trial in second line for TDM1 (GATSBY)

Anti-angiogenic therapy in advanced gastric cancer
- Positive second line for ramucirumab as single agent and with paclitaxel (REGARD, RAINBOW)
- Positive third line for apatinib in Chinese patients
- Negative first line for bevacizumab with cisplatin/5FU and ramucirumab with FOLFOX
- OS results awaited for ramucirumab with cisplatin/5FU (RAINFALL)
THANK YOU