Targeting Angiogenesis in GI Cancers

Kei Muro, MD.

Department of Clinical Oncology
Aichi Cancer Center Hospital
Disclosure

• Kei Muro
  - Consulting or Advisory Role:
    Ono, Merck-Serono
  - Honoraria:
    Taiho, Takeda, Chugai, Merck-Serono, Yakult, Bristol- Myers
  - Research Funding:
    MSD, Daiichi Sankyo, Taiho, Ono, Eli Lilly, Pfizer, Chugai, Merck-Serono, Dainippon Sumitomo, AstraZeneca, GlaxoSmithKline, Quintiles Transnational Japan
MoA of Anti-Angiogenesis And Active Agents for GI malignancies

Aflibercept binds some of VEGF-family

Bevacizumab binds VEGF-A, including subforms

Ramucirumab binds VEGF-A

VEGF-A<sub>121</sub>, VEGF-A<sub>145</sub>, VEGF-A<sub>165</sub>, VEGF-A<sub>189</sub>, VEGF-A<sub>206</sub>

VEGFR1 (Flt-1)

VEGFR2 (Flk-1/KDR)

VEGFR3 (Flt-4)

NRP-1

NRP-2

VEGFR2 (Flt-4)

Aptinib

Regorafenib

Vasculogenesis

Angiogenesis

Lymphangiogenesis

Anti-Angiogenic Agents

Antibody: Bevacizumab*, Aflibercept*, Ramucirumab*


*: FDA approved
Gastric Cancer
Gastric Cancer and Angiogenesis

• VEGF / VEGFR are significant molecular target in gastric cancer\textsuperscript{1,2,3,4}.

• High expression of “VEGF-A”, “VEGF-C”, and “VEGF-D” are related to poor prognosis\textsuperscript{5,6}.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
Survival (%) & Months & \\
\hline
0 & 0 & \\
10 & 10 & \\
20 & 20 & \\
30 & 30 & \\
40 & 40 & \\
50 & 50 & \\
60 & 60 & \\
\hline
\end{tabular}
\end{table}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Survival_Curve.png}
\caption{Correlation between VEGF expression in tumor by IHC and postoperative survival in gastric cancer\textsuperscript{2}}
\end{figure}

\begin{enumerate}
\end{enumerate}
**AVAGAST: A Randomized Double-Blind Placebo-Controlled Phase III Study**

**Locally advanced or metastatic gastric cancer**

**Starting dose of bev/placebo: 30 minutes, subsequent doses: 15 minutes**

**Capecitabine*/Cisplatin (XP)**

- + Placebo q3w

**Capecitabine*/Cisplatin (XP)**

- + Bevacizumab q3w

**Stratification factors:**

1. Geographic region
2. Fluoropirimidine backbone
3. Disease status

*5-FU also allowed if cape contraindicated

Cape 1000 mg/m² oral bid, d1–14, 1-week rest

Cisplatin 80 mg/m² d1

Bevacizumab 7.5 mg/kg d1

Maximum of 6 cycles of cisplatin

Cape and bevacizumab/placebo until PD

AVAGAST: Primary Endpoint Was Not Met

ORR 46% vs 37%, $P = .031$

**Progression-Free Survival**

- **XP + Placebo (n=387)**
  - $HR = 0.80$
  - 95% CI: 0.68–0.93
  - $p = 0.0037$

- **XP + Bev (n=387)**

**Overall Survival**

- **XP + Placebo (n=387)**
  - $HR = 0.87$
  - 95% CI: 0.73–1.03
  - $p = 0.1002$

AVAGAST: Geographic Variation Was Observed by Region in OS

### 1. Differences in subsequent therapy (medical culture/tumor burden)

**AVAGAST: OS Regional Differences Might Be Caused by Differences in Subsequent Tx. Rate**

<table>
<thead>
<tr>
<th>Region</th>
<th>Patients entered</th>
<th>Patients receiving second-line treatment</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia &lt;JPN 24%&gt;</td>
<td>376</td>
<td>248</td>
<td>66</td>
</tr>
<tr>
<td>Europe</td>
<td>249</td>
<td>78</td>
<td>31</td>
</tr>
<tr>
<td>Pan-America</td>
<td>149</td>
<td>32</td>
<td>21</td>
</tr>
</tbody>
</table>

Ceiling Effect of Anti-VEGF?

Progression-Free Survival in 1st Line CRC

<table>
<thead>
<tr>
<th></th>
<th>Kabbinavar 5-FU/LV</th>
<th>Hurwitz IFL</th>
<th>Cassidy XELOX</th>
<th>Cassidy FOLFOX</th>
<th>Fuchs FOLFIRI</th>
<th>Hochster FOLFOX</th>
<th>Hochster XELOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo. + Bev</td>
<td>3.7</td>
<td>4.4</td>
<td>1.9</td>
<td>0.8</td>
<td>3.6</td>
<td>1.2</td>
<td>4.4</td>
</tr>
<tr>
<td>Chemo.</td>
<td>5.5</td>
<td>6.2</td>
<td>7.4</td>
<td>8.6</td>
<td>7.6</td>
<td>8.7</td>
<td>5.9</td>
</tr>
</tbody>
</table>

2. Ceiling effect by Bev
3. Biological differences

pVEGF-A: Potentially Predictive
In mBC, mGC and mPaC

**AViTA (OS) PaC**
- Placebo (low pVEGF-A)
- Placebo (high pVEGF-A)
- Bev (low pVEGF-A)
- Bev (high pVEGF-A)

pVEGF-A low: HR=1.04
pVEGF-A high: HR=0.66
p=0.03

**AVAGAST (OS) GC**
- Placebo (low pVEGF-A)
- Placebo (high pVEGF-A)
- Bev (low pVEGF-A)
- Bev (high pVEGF-A)

pVEGF-A low: HR=1.01
pVEGF-A high: HR=0.72
p=0.07

**AVADO (PFS) BC**
- Placebo (low pVEGF-A)
- Placebo (high pVEGF-A)
- Bev* (low pVEGF-A)
- Bev* (high pVEGF-A)

pVEGF-A low: HR=0.86
pVEGF-A high: HR=0.49
p=0.08

*Bev dose: 7.5 mg/kg

De Haas S, et al. ESMO 2011
### 4. Tumor burden

**AVAGAST: Differences in Patients Baseline Demographics (XP + Placebo Arm)**

<table>
<thead>
<tr>
<th></th>
<th>Japan (%)</th>
<th>ROW (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum size of tumor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 mm</td>
<td>47 (50)</td>
<td>134 (46)</td>
</tr>
<tr>
<td>≥40 mm</td>
<td>18 (19)</td>
<td>97 (33)</td>
</tr>
<tr>
<td><strong>Sum of tumor size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80 mm</td>
<td>31 (33)</td>
<td>113 (39)</td>
</tr>
<tr>
<td>≥80 mm</td>
<td>34 (36)</td>
<td>118 (40)</td>
</tr>
<tr>
<td><strong>Bone metastasis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>5 (5)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Not present</td>
<td>89 (95)</td>
<td>281 (96)</td>
</tr>
<tr>
<td><strong>Peritoneal metastasis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>52 (55)</td>
<td>120 (41)</td>
</tr>
<tr>
<td>No</td>
<td>42 (45)</td>
<td>173 (59)</td>
</tr>
<tr>
<td><strong>Patients with peritoneal limited disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (17)</td>
<td>23 (8)</td>
</tr>
<tr>
<td>No</td>
<td>78 (83)</td>
<td>270 (92)</td>
</tr>
</tbody>
</table>

*Nishina T et al. ASCO-GI, 2012*
**RAINBOW: Study Design**

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

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

* GEJ= gastroesophageal junction; gastric and GEJ will be summarized under the term GC

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Wilke H, et al ASCO-GI, 2014
# RAINBOW: Aspect of Efficacy

## Response

<table>
<thead>
<tr>
<th></th>
<th>RAM + PTX</th>
<th>PBO + PTX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response Rate</strong></td>
<td>28%</td>
<td>16%</td>
</tr>
<tr>
<td><strong>p</strong></td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td><strong>Disease Control Rate</strong></td>
<td>80%</td>
<td>64%</td>
</tr>
<tr>
<td><strong>p</strong></td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

## Progression-Free Survival

<table>
<thead>
<tr>
<th></th>
<th>RAM + PTX</th>
<th>PBO + PTX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients / Events</strong></td>
<td>330 / 279</td>
<td>335 / 296</td>
</tr>
<tr>
<td><strong>Median (mos) (95% CI)</strong></td>
<td>4.40 (4.24, 5.32)</td>
<td>2.86 (2.79, 3.02)</td>
</tr>
</tbody>
</table>

- **Δ mPFS** = 1.5 months

## Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>RAM + PTX</th>
<th>PBO + PTX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients / Events</strong></td>
<td>330 / 256</td>
<td>335 / 260</td>
</tr>
<tr>
<td><strong>Median (mos) (95% CI)</strong></td>
<td>9.63 (8.48, 10.81)</td>
<td>7.36 (6.31, 8.38)</td>
</tr>
</tbody>
</table>

- **Δ mOS** = 2.3 months

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Forest Plots for Subgroup Univariate Analyses by Geographic Region in terms of OS / PFS

Overall Survival

Geographic region
1: North America, Europe, Australia
2: South America
3: Asia

Progression-Free Survival

REGARD Trial

- **N=355**
  - Gastric/GEJ, adenocarcinoma
  - Prior FU or platinum as 1st line therapy
  - ECOG PS0-1
  - Age: >18

Randomization

- **RAM 8mg/kg (day 1, 15)**
  - + Best Supportive Care
  - Repeated every 2 weeks

- **Placebo (day 1, 15)**
  - + Best Supportive Care
  - Repeated every 2 weeks

Primary endpoint: Overall Survival (OS)
Secondary endpoints:
- Progression-free Survival (PFS), ORR, Safety, QOL
- (EORTC QLQ-C30∙EQ-5D), ramucirumab immunogenicity, etc.
REGARD: Aspect of Efficacy

**Progression-Free Survival**

<table>
<thead>
<tr>
<th></th>
<th>mPFS</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramucirumab</td>
<td>2.1 M</td>
<td>0.483</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.3 M</td>
<td><em>P&lt;0.0001</em></td>
</tr>
</tbody>
</table>

*: Stratified Log-rank

**Overall Survival**

<table>
<thead>
<tr>
<th></th>
<th>MST</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramucirumab</td>
<td>5.2 M</td>
<td>0.776</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.8 M</td>
<td><em>p=0.047</em></td>
</tr>
</tbody>
</table>

*: Stratified Log-rank

**Objective Tumor Response**

<table>
<thead>
<tr>
<th>Response Type</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.

**STO3: Design and Results**

- **3-year OS (95% CI)**
  - ECX: 48.9% (43.6% to 53.8%)
  - ECX+B: 47.6% (42.3% to 52.7%)

**Histologically confirmed, resectable (MDT review) stage Ib-IV adenocarcinoma of the lower oesophagus, OGJ or stomach**

- Randomised 1:1
  - ECX
    - ECX: 3 cycles
    - 5-6 week break
  - ECX + Bevacizumab
    - ECX + Bevacizumab: 3 cycles
    - 6-10 week break
  - Surgery
  - ECX: 3 cycles
  - ECX + Bevacizumab: 3 cycles
  - Maintenance Bevacizumab
    - 6 doses

**No difference in clinical response and TRG**

- Similar 30 and 90 days mortality but an elevated rate of post-operative anastomotic leak and deaths in this group

**HR (95% CI) = 1.067 (0.8911, 1.279)**

**Log rank p-value = 0.4784**
# VEGF Targeting Therapy in Gastric Cancer: Phase III Trials

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Target</th>
<th>Design</th>
<th>HR OS</th>
<th>HR PFS</th>
<th>RR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 L</td>
<td>STO3</td>
<td>VEGF-A</td>
<td>ECX +/- Bev</td>
<td>1.07*</td>
<td>1.03*</td>
</tr>
<tr>
<td>1st L</td>
<td>AVAGAST</td>
<td>VEGFR2</td>
<td>XP +/- Bev</td>
<td>0.87*</td>
<td>0.8**</td>
</tr>
<tr>
<td>2nd L</td>
<td>RAINBOW</td>
<td>VEGFR2</td>
<td>Paclitaxel +/- RAM</td>
<td>0.81**</td>
<td>0.63**</td>
</tr>
<tr>
<td>2nd L</td>
<td>REGARD</td>
<td>VEGFR2</td>
<td>BSC +/- RAM</td>
<td>0.78**</td>
<td>0.48**</td>
</tr>
<tr>
<td>3rd L+</td>
<td>Apatinib</td>
<td>VEGFR2</td>
<td>BSC +/- Apatinib</td>
<td>0.71**</td>
<td>0.44**</td>
</tr>
</tbody>
</table>

*: Not significant  
**: Statistically significant

Al-Batran SE: ESMO 2015
**Analysis of \( C_{min,1} \) and Overall Survival**

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>RAM+PAC N/#events</th>
<th>PBO+PAC N/#events</th>
<th>Median (months)</th>
<th>Hazard Ratio* (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAINBOW OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBO+PAC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAM+PAC Q1</td>
<td>80/68</td>
<td>335/260</td>
<td>7.4</td>
<td>1.04 (0.79, 1.37)</td>
<td>0.7891</td>
</tr>
<tr>
<td>RAM+PAC Q2</td>
<td>80/67</td>
<td>335/260</td>
<td>8.6</td>
<td>0.84 (0.64, 1.11)</td>
<td>0.2168</td>
</tr>
<tr>
<td>RAM+PAC Q3</td>
<td>80/58</td>
<td>335/260</td>
<td>11.0</td>
<td>0.69 (0.51, 0.92)</td>
<td>0.0107</td>
</tr>
<tr>
<td>RAM+PAC Q4</td>
<td>81/57</td>
<td>335/260</td>
<td>12.9</td>
<td>0.53 (0.40, 0.71)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- Logistic regression analysis indicated that patients with higher RAM exposure may be associated with an increased risk of grade \( \geq 3 \) hypertension, neutropenia, or leukopenia. No apparent trend was observed for febrile neutropenia or fatigue/asthenia.

---

**Grade \( \geq 3 \) Adverse Events by Quartile**

<table>
<thead>
<tr>
<th>C( _{min,1} ) concentration range, ( \mu g/mL )</th>
<th>Overall</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=335</td>
<td>11.6 to 76.7</td>
<td>11.6 to ( \leq 22.8 )</td>
<td>&gt;22.8 to ( \leq 28.0 )</td>
<td>&gt;28.0 to ( \leq 35.5 )</td>
<td>&gt;35.5 to 76.7</td>
</tr>
</tbody>
</table>

**Hypertension, \( * \), %**
- PBO+PAC: 3.0
- Overall: 14.6
- Q1: 9.9
- Q2: 17.5
- Q3: 15.0
- Q4: 16.2

**Neutropenia, %**
- PBO+PAC: 20.9
- Overall: 42.1
- Q1: 25.9
- Q2: 35.0
- Q3: 47.5
- Q4: 60.0

**Febrile neutropenia, %**
- PBO+PAC: 2.7
- Overall: 3.1
- Q1: 3.7
- Q2: 1.3
- Q3: 3.8
- Q4: 3.8

**Leukopenia, %**
- PBO+PAC: 7.2
- Overall: 17.8
- Q1: 13.6
- Q2: 11.2
- Q3: 22.5
- Q4: 23.8

**Fatigue/asthenia, %**
- PBO+PAC: 5.4
- Overall: 12.1
- Q1: 11.1
- Q2: 11.3
- Q3: 13.8
- Q4: 12.5

---

Future Perspective: Ongoing 1\textsuperscript{st} Line Therapy

**Japanese Phase Ib Trial**
- HER2 -ve, Advanced Gastric Ca. (N=18)
- RAM + XP cohort
- RAM + SOX cohort
- RAM + SP cohort

**Asian Phase II Trial: RAINSTORM**
- HER2 -ve, AGC (N=190)
- PBO + SOX
- RAM + SOX
- RAM + PTX

**Global Phase III Trial: RAINFALL**
- HER2 -ve, AGC (N=616)
- PBO + XP
- RAM + XP

Clinical Trials. gov: NCT02359058
Clinical Trials. gov: NCT02539225
Clinical Trials. gov: NCT02314117
Clinical Trials. gov: NCT02314117

Dose dense based on Exposure Response
Colorectal Cancer
<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>ORR</th>
<th>PFS (Mon.)</th>
<th>OS (Mon.)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVF2107g (n = 813)</td>
<td>IFL ± Bevacizumab</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Hurwitz et al., NEJM 2004</td>
</tr>
<tr>
<td>NO 16966 (n = 1401)</td>
<td>XELOX / FOLFOX ± Bevacizumab</td>
<td>−</td>
<td>✓</td>
<td>−</td>
<td>Saltz et al., JCO 2008</td>
</tr>
<tr>
<td>Kabbinavar (n = 490)</td>
<td>5-FU/LA (or IFL ) ± Bevacizumab</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Kabbinavar et al., JCO 2005</td>
</tr>
<tr>
<td>CRYSTAL (n = 666)*</td>
<td>FOLFIRI ± Cetuximab*</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Van Cutsem et al., NEJM 2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Van Cutsem et al., JCO 2011</td>
</tr>
<tr>
<td>OPUS (n = 179)*</td>
<td>FOLFOX4 ± Cetuximab*</td>
<td>✓</td>
<td>✓</td>
<td>−</td>
<td>Bokemeyer et al., JCO 2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bokemeyer et al., Ann Oncol 2011</td>
</tr>
<tr>
<td>PRIME (n = 656)*</td>
<td>FOLFOX ± Panitumumab*</td>
<td>✓</td>
<td>✓</td>
<td>−</td>
<td>Douillard et al., JCO 2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Douillard et al., ASCO 2011</td>
</tr>
</tbody>
</table>

 ✓ Statistically significant, − Not significant, *
: KRAS wildtype population
VEGF Is An Early And Persistent Promoter of Tumour Angiogenesis

- Tumors continually require VEGF to recruit new vasculature.
- VEGF continues to be expressed throughout tumor progression, even as secondary pathways emerge.

References:
# Efficacy in 2\textsuperscript{nd} Line Trials Using Anti-Angiogenesis for mCRC

<table>
<thead>
<tr>
<th></th>
<th>E3200 FOLFOX vs. FOLFOX+Bev</th>
<th>VELOUR FOLFIRI+PBO vs. FOLFIRI+Afli</th>
<th>TML Chemo vs. Chemo+Bev</th>
<th>RAISE FOLFIRI+PBO vs. FOLFIRI+RAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior BV(%)</td>
<td>0%</td>
<td>30%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>N</td>
<td>577</td>
<td>1226</td>
<td>820</td>
<td>1072</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>OS</td>
<td>OS</td>
<td>OS</td>
<td>OS</td>
</tr>
<tr>
<td>PFS (Mos)</td>
<td>4.7 vs. 7.3 HR:0.61 p&lt;0.0001</td>
<td>4.7 vs. 6.9 HR:0.758 p&lt;0.0001</td>
<td>4.1 vs. 5.7 HR:0.68 p&lt;0.0001</td>
<td>4.5 vs. 5.7 HR:0.79 p=0.0005</td>
</tr>
<tr>
<td>OS (Mos)</td>
<td>10.8 vs. 12.9 HR:0.75 p=0.0011</td>
<td>12.1 vs. 13.5 HR:0.817 p=0.0032</td>
<td>9.8 vs. 11.2 HR:0.81 p=0.0062</td>
<td>11.7 vs. 13.3 HR:0.84 p=0.0219</td>
</tr>
<tr>
<td>RR (%)</td>
<td>8.6 vs. 22.7 p&lt;0.0001</td>
<td>11.1 vs. 19.8 p&lt;0.001</td>
<td>4 vs. 5 p=0.31</td>
<td>12.5 vs. 13.4 p=0.6336</td>
</tr>
</tbody>
</table>

Giantonio te al. JCO 2007
Van Cutsem et al. JCO 2012
Bennouna et al. Lancet Oncol 2013
Tabernero et al. Lancet Oncol 2015
VEGF-Axis Dependent And Non-VEGF Mediated Mechanisms of Resistance to Anti-Angiogenic Therapies

CORRECT: Regorafenib vs. Placebo for mCRC after Failure of Standard Therapy

Primary endpoint met prespecified stopping criteria at interim analysis (1-sided $p<0.009279$ at approximately 74% of events required for final analysis)

All patients have received prior bevacizumab

Anti-Angiogenesis Therapy for GI Cancer: Small Benefit in Earlier Line

Stomach Cancer
- Bev: STO-3
- Bev: AVAGAST
- RAM: RAINBOW
- Apatinib

Colorectal Cancer
- Bev: NSABP C-08
- Bev: AVANT
- Bev: AVF2107g
- Bev: NO16966
- Bev: E3200
- Afli: VELOUR
- RAM: RAISE
- REG: CORRECT
- REG: CONCUR

Disease setting
- Localized
- Locally advanced
- 1st
- 2nd
- 3rd - Advanced

Impact: O: Impact in OS
Δ: Impact in PFS
×: No Impact in OS/DFS/PFS

Yoon HH, ASCO-GI 2015, substantially modified
Summary: Anti-Angiogenesis for GI Cancers

- Effective in targeting anti-angiogenesis for GI cancers

- Gastric cancer
  - Positive role of anti-angiogenesis therapy as 2nd line or later
  - So far, no role of that as 1st line or early stage treatment
    - Next step

- Colorectal cancer
  - Positive role of anti-angiogenesis therapy in all lines
  - Also, active in continuing beyond progression (e.g. BBP, RAM, REG)
    - No role of early stage treatment

However, ...

- Statistical significance ≠ Meaningful clinical benefit
- Cost effectiveness? (Pandora’s box)

For the above reasons,

- Next challenges are strongly needed and absolutely crucial
Future Directions

Anti-Angiogenesis for GI Cancers

To achieve meaningful survival benefit ...

- Predictive biomarkers (pVEGFA?, others)
  - Need further investigation

- Maintenance therapy (should learn from NSCLC)
  - Although difficult to establish appropriate endpoint ...

- Enhancement of efficacy (exposure response of ramucirumab)
  - Prospective RCT needed

- Promising interaction of anti-angiogenesis therapy
  - combined with other targeting agents, immune checkpoint inhibitors ...
Acknowledgement

Thank you for your kind attention
Back Up
AVAGAST: Correlation between Efficacy Outcomes and Baseline pVEGF-A by Region (Biomarker Population)

<table>
<thead>
<tr>
<th>Population</th>
<th>pVEGF-A*</th>
<th>Patients, n</th>
<th>Events, n</th>
<th>Hazard ratio† [95% CI]</th>
<th>P value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>Low</td>
<td>357</td>
<td>224</td>
<td>1.01 [0.77;1.31]</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>355</td>
<td>252</td>
<td>0.72 [0.57;0.93]</td>
<td></td>
</tr>
<tr>
<td>Non-Asia†</td>
<td>Low</td>
<td>143</td>
<td>96</td>
<td>1.01 [0.68;1.51]</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>202</td>
<td>146</td>
<td>0.59 [0.43;0.82]</td>
<td></td>
</tr>
<tr>
<td>Asia-Pacific</td>
<td>Low</td>
<td>214</td>
<td>128</td>
<td>0.99 [0.70;1.40]</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>153</td>
<td>106</td>
<td>0.92 [0.63;1.34]</td>
<td></td>
</tr>
<tr>
<td>Progression-free survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>Low</td>
<td>357</td>
<td>254</td>
<td>0.86 [0.67;1.10]</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>355</td>
<td>263</td>
<td>0.66 [0.52;0.85]</td>
<td></td>
</tr>
<tr>
<td>Non-Asia†</td>
<td>Low</td>
<td>143</td>
<td>99</td>
<td>0.85 [0.57;1.26]</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>202</td>
<td>143</td>
<td>0.54 [0.39;0.76]</td>
<td></td>
</tr>
<tr>
<td>Asia-Pacific</td>
<td>Low</td>
<td>214</td>
<td>155</td>
<td>0.86 [0.63;1.18]</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>153</td>
<td>120</td>
<td>0.87 [0.61;1.25]</td>
<td></td>
</tr>
</tbody>
</table>

**“High” indicates above the median value (111 pg/mL), and “low” indicates less than or equal to the median**

†Hazard ratio for bevacizumab plus chemotherapy vs. placebo plus chemotherapy

‡Europe, and North and South America

Shah, et al. ECCO-ESMO 2011 (abstract 1415)
Metastatic Gastric Cancer in 2nd Line
According to Japanese Guideline 2015

Most Preferred Regimen
Ramucirumab + Paclitaxel

Preferred Regimen
Paclitaxel Monotherapy (Mono.)
Docetaxel Mono.
Irinotecan Mono.
Ramucirumab Mono.
# Treatment Pathways Currently under Evaluation as Phase III Trials for Gastric Cancer

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET?</td>
<td>(Rilotumumab ×, Onartuzumab ×)</td>
</tr>
<tr>
<td>EGFR?</td>
<td>(Panitumumab ×, Cetuximab ×)</td>
</tr>
<tr>
<td>HER2</td>
<td>(Trastuzumab○, T-DM1 ×, Lapatinib ×)</td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>(Bev ×, RAM○)</td>
</tr>
<tr>
<td>PARP</td>
<td></td>
</tr>
<tr>
<td>STAT3</td>
<td></td>
</tr>
<tr>
<td>Checkpoint Inhibitor</td>
<td></td>
</tr>
</tbody>
</table>

>5,000 patients are planned to be enrolled in 19 ongoing studies, with additional studies being planned

Shah MA. J Clin Oncol 33:1760–1769, 2015, substantially modified
Efficacy in 1st Line: Bevacizumab vs. Cetuximab

**CALGB 80405 / FIRE-3**

**CALGB (RAS WT): Δ mOS = 0.8 months**

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo + BEV</td>
<td>256</td>
<td>31.2 (26.9-34.3)</td>
<td>0.9 (0.7-1.1)</td>
<td>0.40</td>
</tr>
<tr>
<td>Chemo + Cmab</td>
<td>270</td>
<td>32.0 (27.6-38.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIRE-3 (RAS WT): Δ mOS = 8.1 months**

<table>
<thead>
<tr>
<th>Events n/N (%) median (months) 95% CI</th>
<th>HR (95% CI)</th>
<th>p (log-rank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[107/199</td>
<td>33.1</td>
<td>24.5-39.4</td>
</tr>
<tr>
<td>[133/201</td>
<td>25.0</td>
<td>23.0-28.1</td>
</tr>
</tbody>
</table>

**Primary Endpoint (PE)**
- **CALGB 80405**: Overall Survival
- **FIRE-3**: Response rate

**Countries**
- **CALGB 80405**: USA, Canada
- **FIRE-3**: German, Austria

**Results**
- **CALGB 80405**: Negative (PE not met)
- **FIRE-3**: Negative (PE not met)

**Number of RAS WT**
- **CALGB 80405**: 526
- **FIRE-3**: 400

**Number of events (%)**
- **CALGB 80405**: 355 (67.5%)
- **FIRE-3**: 240 (60.0%)

**% of Subsequent therapy**
- **CALGB 80405**: 88%
- **FIRE-3**: 67%
Preop. FLOT Is Associated with Significantly Higher Rates of pCR Than ECF/ECX

**FLOT4 Study Design**

- Gastric cancer or adenocarcinoma of the gastro-esophageal junction type I-III
- Medically and technically operable stages
- T2-4, every N, M0 or every T, N+, M0

**Pathological Remission with ECF/ECX vs. FLOT — Central Evaluation, ITT group**

<table>
<thead>
<tr>
<th>Pathological regression</th>
<th>ECF/ECX n(%)</th>
<th>FLOT n(%)</th>
<th>P-Value (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete (pCR)</td>
<td>8</td>
<td>20</td>
<td>0.015</td>
</tr>
<tr>
<td>Subtotal (pSR)</td>
<td>23</td>
<td>27</td>
<td>0.015</td>
</tr>
<tr>
<td>pCR+pSR</td>
<td>31</td>
<td>47</td>
<td>0.015</td>
</tr>
<tr>
<td>Partial (pPR)</td>
<td>28</td>
<td>23</td>
<td>0.015</td>
</tr>
<tr>
<td>Minor (pMR)</td>
<td>44</td>
<td>45</td>
<td>0.015</td>
</tr>
<tr>
<td>No response (pNR)</td>
<td>8</td>
<td>4</td>
<td>0.015</td>
</tr>
<tr>
<td>Not resectable</td>
<td>26</td>
<td>9</td>
<td>0.015</td>
</tr>
</tbody>
</table>

*primary Endpoint phase II
Next Challenge: AIO-STO-0315 RAMSES

Perioperative Ramucirumab in combination with FLOT versus FLOT alone for resectable esophagogastric adenocarcinoma – A phase II/III trial of the AIO

Inclusion (Selection)
- Adenocarcinoma of the stomach or GEJ
- HER2 negative
- ECOG PS: 0-2
- No distant metastasis

Stratification
- Age: 18-69 vs. 70<
- Tumor site: GEJ vs. gastric
- Clinical stage:
  T1/2 vs. T3/4 & N- vs. N+

Phase II: N=150
Phase III: N=758

Arm A
- FLOT; q 2 weeks, 4 cycles
  ↓
  Surgery
  ↓
  FLOT; q 2 weeks, 4 cycles

Arm B
- FLOT + Ram; q 2 weeks, 4 cycles
  ↓
  Surgery
  ↓
  FLOT + Ram; q 2 weeks, 4 cycles
  ↓
  Ram; q 2 weeks, 16 cycles

Based on preop. FLOT showed significantly higher rates of pCR than ECF/ECX in 2015 ESMO