Targeted Therapies in Gastric Cancer: Where Do We Stand Today

Yoon-Koo Kang
Asan Medical Center, University of Ulsan
Seoul, Korea
Chemotherapy is the standard of care in advanced gastric cancer.

Median OS (months)

FAMTX 1 (n=30) BSC 1 (n=10)
FEMTX 2 (n=21) BSC 2 (n=20)
ELF 3 (n=10) BSC 3 (n=8)
ELF 4 (n=52) BSC 4 (n=51)

Combination better than single agent
Meta-Analysis in AGC

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Combination Chemotherapy</th>
<th>No. Single-Agent Chemotherapy</th>
<th>Hazard Ratio (fixed)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cullinan 1985</td>
<td>51</td>
<td>51</td>
<td>0.90, 0.61 to 1.33</td>
<td></td>
</tr>
<tr>
<td>De Lisi 1986</td>
<td>42</td>
<td>43</td>
<td>1.16, 0.26 to 5.15</td>
<td></td>
</tr>
<tr>
<td>Levi 1986</td>
<td>94</td>
<td>93</td>
<td>0.58, 0.43 to 0.77</td>
<td></td>
</tr>
<tr>
<td>Cullinan 1994</td>
<td>183</td>
<td>69</td>
<td>0.90, 0.69 to 1.16</td>
<td></td>
</tr>
<tr>
<td>Loehrer 1994</td>
<td>64</td>
<td>94</td>
<td>0.85, 0.61 to 1.19</td>
<td></td>
</tr>
<tr>
<td>Colucci 1995</td>
<td>35</td>
<td>36</td>
<td>0.70, 0.42 to 1.16</td>
<td></td>
</tr>
<tr>
<td>Barone 1998</td>
<td>36</td>
<td>36</td>
<td>0.89, 0.55 to 1.42</td>
<td></td>
</tr>
<tr>
<td>Yamamura 1998</td>
<td>37</td>
<td>34</td>
<td>0.88, 0.55 to 1.41</td>
<td></td>
</tr>
<tr>
<td>Popov 2002</td>
<td>30</td>
<td>30</td>
<td>0.86, 0.32 to 2.29</td>
<td></td>
</tr>
<tr>
<td>Ohtsu 2003</td>
<td>175</td>
<td>105</td>
<td>1.04, 0.82 to 1.32</td>
<td></td>
</tr>
<tr>
<td>Bouche 2004</td>
<td>89</td>
<td>45</td>
<td>0.65, 0.45 to 0.95</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>836</td>
<td>636</td>
<td>0.83, 0.74 to 0.93</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 12.30, (P = .27)$
Test for overall effect: $Z = 3.28 (P = .001)$

OS with recent combination chemotherapies in metastatic / recurrent gastric cancer

- FAMTX
- IF
- CF
- DCF
- ECF
- ECX
- EOX
- FP
- XP
- SP
- SP

Recent Combos + Targeted therapy has opened a new era in gastric cancer treatment.
ToGA Trial: Addition of Trastuzumab to XP/FP improved OS in Metastatic GC

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>Median OS</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab + XP/FP</td>
<td>167</td>
<td>13.8 mo</td>
<td>0.74</td>
<td>0.60, 0.91</td>
<td>0.0046</td>
</tr>
<tr>
<td>XP/FP</td>
<td>182</td>
<td>11.1 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Van Cutsem, Kang, ---, Bang. 2009 ASCO
4 Months of Survival Benefit with Trastuzumab in IHC 2+/FISH+ or IHC 3+ patients

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>Median OS</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>120</td>
<td>16.0 mo</td>
<td>0.65</td>
<td>0.51, 0.83</td>
</tr>
<tr>
<td>XP/FP</td>
<td>136</td>
<td>11.8 mo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Van Cutsem, Kang, ---, Bang. 2009 ASCO
Rationale for Trastuzumab Treatment for HER2-positive GC

- Trastuzumab, a humanized moAb against HER2
  - Prevents HER2 activation by blocking cleavage of the extracellular domain

- Trastuzumab has a proven survival benefit in HER2-positive breast cancer

- HER2 positivity demonstrated in 7–34% of GCs

- Trastuzumab is effective against HER2-overexpressing GC cell lines in vitro

ToGA trial design

- Phase III, randomised, open-label, international, multicentre study

**Screening for HER2 positivity** → **HER2-positive advanced GC** → **R**

- Capecitabine or 5-FU* + cisplatin (XP/FP)
- Capecitabine or 5-FU* + cisplatin (XP/FP) + trastuzumab

**Stratification factors**
- Advanced vs metastatic
- GC vs GEJ
- Measurable vs non-measurable
- ECOG PS 0-1 vs 2
- Capecitabine vs 5-FU

Primary endpoint = overall survival

*Chosen at investigator’s discretion
5-FU, 5-fluorouracil; FP, 5-FU plus cisplatin; R, randomised; XP, capecitabine and cisplatin
Rationale for choosing XP / FP
: ML17032 : Good Efficacy

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FP</td>
<td>137</td>
<td>29%</td>
<td>5.0 mos</td>
<td>9.3 mos</td>
</tr>
<tr>
<td>XP</td>
<td>139</td>
<td>41%</td>
<td>5.6 mos</td>
<td>10.5 mos</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></td>
<td></td>
<td>0.81 (0.63–1.04)</td>
<td>0.85 (0.64–1.13)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.03</td>
<td>0.0008 *</td>
<td>&lt;0.008*</td>
<td></td>
</tr>
</tbody>
</table>

* Compared to 1.25, non-inferiority upper limit of HR

Rationale for choosing XP / FP: ML17032: Favorable Safety

Patients (%)

Grade 3-4 Toxicities

- Neutropenia
- Vomiting
- Stomatitis
- Diarrhea
- Anemia
- HFS
- Leucopenia
- Nausea

HER2 positivity 22.1% according to protocol (based on 3,667 successful screenings)
## Patient demographics and baseline characteristics in ToGA trial

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>XP/FP (n=290)</th>
<th>Trastuzumab + XP/FP (n=294)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female), %</td>
<td>75/25</td>
<td>77/23</td>
</tr>
<tr>
<td>Age, median (range) years</td>
<td>59 (21–82)</td>
<td>61 (23–83)</td>
</tr>
<tr>
<td>Weight, median (range) kg</td>
<td>60.3 (28–105)</td>
<td>61.45 (35–110)</td>
</tr>
<tr>
<td>Region, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>166 (56)*</td>
<td>158 (53)†</td>
</tr>
<tr>
<td>C/S America</td>
<td>26 (9)*</td>
<td>27 (9)†</td>
</tr>
<tr>
<td>Europe</td>
<td>95 (32)*</td>
<td>99 (33)†</td>
</tr>
<tr>
<td>Other</td>
<td>9 (3)*</td>
<td>14 (5)†</td>
</tr>
<tr>
<td>Type of GC, % (central assessment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinal</td>
<td>74.2‡</td>
<td>76.8§</td>
</tr>
<tr>
<td>Diffuse</td>
<td>8.7‡</td>
<td>8.9§</td>
</tr>
<tr>
<td>Mixed</td>
<td>17.1‡</td>
<td>14.3§</td>
</tr>
<tr>
<td>Prior gastrectomy, %</td>
<td>21.4</td>
<td>24.1</td>
</tr>
</tbody>
</table>

- Highest recruitment was from Korea, Japan, China and Russia

* n=296; † n=298; ‡ n=287; § n=293
Significant improvements in all efficacy parameters with Trastuzumab

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>XP/FP (n=290)</th>
<th>Trastuzumab + XP/FP (n=294)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS, median months</td>
<td>11.1</td>
<td>13.8</td>
<td>0.74</td>
<td>(0.60, 0.91)</td>
</tr>
<tr>
<td>PFS, median months</td>
<td>5.5</td>
<td>6.7</td>
<td>0.71</td>
<td>(0.59, 0.85)</td>
</tr>
<tr>
<td>TTP, median months</td>
<td>5.6</td>
<td>7.1</td>
<td>0.70</td>
<td>(0.58, 0.85)</td>
</tr>
<tr>
<td>ORR, %</td>
<td>34.5</td>
<td>47.3</td>
<td>1.70*</td>
<td>(1.22, 2.38)</td>
</tr>
<tr>
<td>Patients with measurable disease</td>
<td>37.4</td>
<td>50.9</td>
<td>1.74*</td>
<td>(1.23, 2.46)</td>
</tr>
<tr>
<td>DoR, median months</td>
<td>4.8</td>
<td>6.9</td>
<td>0.54</td>
<td>(0.40, 0.73)</td>
</tr>
<tr>
<td>Clinical benefit rate, %</td>
<td>69.3</td>
<td>78.9</td>
<td>1.66*</td>
<td>(1.14, 2.41)</td>
</tr>
</tbody>
</table>
Overall survival by HER2 status

### Pre-planned analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Median OS (mo)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>584</td>
<td>11.1 vs 13.8</td>
<td>0.74</td>
<td>0.60, 0.91</td>
</tr>
<tr>
<td>IHC 0/FISH+</td>
<td>61</td>
<td>7.2 vs 10.6</td>
<td>0.92</td>
<td>0.48, 1.76</td>
</tr>
<tr>
<td>IHC 1+/FISH+</td>
<td>70</td>
<td>10.2 vs 8.7</td>
<td>1.24</td>
<td>0.70, 2.20</td>
</tr>
<tr>
<td>IHC 2+/FISH+</td>
<td>159</td>
<td>10.8 vs 12.3</td>
<td>0.75</td>
<td>0.51, 1.11</td>
</tr>
<tr>
<td>IHC 3+/FISH+</td>
<td>256</td>
<td>12.3 vs 17.9</td>
<td>0.58</td>
<td>0.41, 0.81</td>
</tr>
<tr>
<td>IHC 3+/FISH−</td>
<td>15</td>
<td>17.7 vs 17.5</td>
<td>0.83</td>
<td>0.20, 3.38</td>
</tr>
</tbody>
</table>

### Exploratory analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Median OS (mo)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC 0 or 1+/FISH+</td>
<td>131</td>
<td>8.7 vs 10.0</td>
<td>1.07</td>
<td>0.70, 1.62</td>
</tr>
<tr>
<td>IHC 2+/FISH+ or IHC 3+</td>
<td>446</td>
<td>11.8 vs 16.0</td>
<td>0.65</td>
<td>0.51, 0.83</td>
</tr>
</tbody>
</table>

Interaction of treatment effect with HER2 result in exploratory analysis, \( p=0.0368 \)
Similar safety profile for XP/FP ± Trastuzumab

Grade 3/4 AEs in >5% of patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>XP/FP + Herceptin (n=294)</th>
<th>XP/FP (n=290)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Anaemia</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Anorexia</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Asthenia</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Safety population
Trastuzumab does not add significant cardiac toxicity to XP/FP

<table>
<thead>
<tr>
<th>Cardiac adverse event, n (%)</th>
<th>XP/FP n=290</th>
<th>Trastuzumab + XP/FP n=294</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac AEs, total</td>
<td>18 (6)</td>
<td>17 (6)</td>
</tr>
<tr>
<td>All grades</td>
<td>Grade 3/4</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>All grades</td>
<td>Grade 3/4</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>LVEF drops*, asymptomatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50%</td>
<td>2 (1.1)</td>
<td>14 (5.9)</td>
</tr>
<tr>
<td>&lt;50% and by ≥10%</td>
<td>2 (1.1)</td>
<td>11 (4.6)</td>
</tr>
<tr>
<td>Cardiac AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>leading to death</td>
<td>2 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Cardiac arrest;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cardio-respiratory arrest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute MI; unstable angina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and cardiac failure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Measured at baseline and every 12 weeks; MI, myocardial infarction
Conclusions of ToGA trial

- Addition of Trastuzumab to cytotoxic chemotherapy could significantly improve the efficacy of chemotherapy without increased toxicities.

- Trastuzumab in combination with chemotherapy can now be considered a new standard of care for patients with HER2-positive advanced gastric or GE junction adenocarcinoma.

- HER2 screening is highly recommended in patients with gastric cancer.
Targeted Therapies in Solid Tumors

Focus of interest

Targeting angiogenesis
- Monoclonal Abs
  - Bevacizumab
  - VEGF-trap
- Small molecule TKIs
  - Sunitinib
  - Sorafenib

Targeting the EGFR pathway
- Small molecule TKIs
  - Gefitinib
  - Erlotinib
  - Lapatinib
- Monoclonal Abs
  - Cetuximab
  - Panitumumab
  - Trastuzumab
EGFR in gastric cancer

- Overexpression of EGFR is common in gastric cancer
  - 86% of 42 tumour samples (stomach, GEJ) + 59.5% of 42 gastric cancer samples EGFR expressing by IHC *(JCO2006; 24:4922-4927; ASCO2007 #4526)*
  - 62% of 51 examined gastric adenocarcinomas exhibited an EGFR expression by RT-PCR *(World J Gastroenterol 2007; 13:3605-3609)*

- Increased EGFR expression linked to:
  - advanced clinical stage + presence of lymph node metastasis
  - decreased survival in 3 out of 6 studies *(EJC 2001; 37:S9-S15)*
TKIs targeting EGFR: Phase II Studies in AGC

<table>
<thead>
<tr>
<th>Targeted Agents</th>
<th>Combined Chemotx</th>
<th>N</th>
<th>RR</th>
<th>TTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib¹</td>
<td>-</td>
<td>71</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Erlotinib²</td>
<td>-</td>
<td>68</td>
<td>9% EGJ 0% GC</td>
<td>2 mo EGJ 1.6 mo GC</td>
</tr>
</tbody>
</table>

Cetuximab: a partially humanized murine IgG1 moAb against EGFR

<table>
<thead>
<tr>
<th>Combined Chemotx</th>
<th>N</th>
<th>RR</th>
<th>mTTP/PFS</th>
<th>mOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI&lt;sup&gt;1&lt;/sup&gt;</td>
<td>38</td>
<td>44%</td>
<td>8.0 mo</td>
<td>16.0 mo</td>
</tr>
<tr>
<td>FOLFOX6&lt;sup&gt;2&lt;/sup&gt;</td>
<td>38</td>
<td>50%</td>
<td>5.5 mo</td>
<td>9.9 mo</td>
</tr>
<tr>
<td>FUFOX&lt;sup&gt;3&lt;/sup&gt;</td>
<td>46</td>
<td>65%</td>
<td>7.6 mo</td>
<td>9.5 mo</td>
</tr>
<tr>
<td>XELOX&lt;sup&gt;4&lt;/sup&gt;</td>
<td>44</td>
<td>52%</td>
<td>6.5 mo</td>
<td>11.8 mo</td>
</tr>
</tbody>
</table>

2. Han, et al. Br J Cancer 2009,  
3. Lordick, et al. Br J Cancer 2010,  
Cetuximab: Phase III Trial for 1st line AGC: EXPAND

- Primary endpoint: Superiority in PFS
- N = 870 patients with gastric or GEJ adenocarcinoma, for 1st line palliative chemotherapy

<table>
<thead>
<tr>
<th>Cetuximab</th>
<th>400mg/m² initial dose, then 250mg/m² per week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>80mg/m² iv D1</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>1000mg/m² bid po D1-14 q3w</td>
</tr>
</tbody>
</table>

- Cetuximab: Phase III Trial for 1st line AGC: EXPAND
- Primary endpoint: Superiority in PFS
- N = 870 patients with gastric or GEJ adenocarcinoma, for 1st line palliative chemotherapy
Panitumumab: Phase III Trial in Esophagogastric Cancer: REAL-3

Locally advanced or metastatic esophagogastric adenocarcinoma N=730

- Panitumumab (Vectibix): a fully humanized IgG2 moAb against EGFR
- Primary endpoint: overall survival

EOX + Panitumumab

EOX

Every 3 weeks
HER2 targeting TKI: Lapatinib (Tykerb)

- A small molecule tyrosine kinase inhibitor selectively targeting ErbB1 (EGFR) and ErbB2 (HER2) in vitro and in vivo
  - Inhibition of 1 receptor type alone might not be sufficient for optimal inhibition of tumor cell growth and survival
  - ErbB receptors initiate signal transduction through multiple combinatorial interactions (homodimerization and heterodimerization)

- Proven effective in HER2 positive breast cancer patients after failure of Trastuzumab
Lapatinib: Phase II study of Monotherapy for AGC (SWOG 0413)

- 46 patients for 1st line palliative treatment
  - No HER2 selection
- Lapatinib 1500 mg po qd
- 3 cPR + 2 uc PR + 9 SD
- Median TTF = 2 mo, Median OS = 5 mo
- Toxicities
  - 9 G3 fatigue
  - 7 G3 anorexia
  - 4 G3 diarrhea
  - 1 G4 cardiac infarction

Iqbal, et al. 2007 ASCO
Lapatinib: Phase III Trial for 1st line AGC: LoGIC

- Primary endpoint: PFS
- N = 410 Advanced gastric, GEJ, or esophageal adenocarcinoma with erbB2 overexpression, for 1st line palliative chemotherapy

R

- Oxaliplatin 130 mg/m² iv D1, q 3 weeks X 8 cycles
- Capecitabine 850 mg/m² bid po D1-14 q 3 weeks
- Lapatinib 1250 mg po daily

Placebo po daily
Primary endpoint: OS
N = 314 Advanced gastric, GEJ adenocarcinoma with erbB2 overexpression after failure of 1st line palliative chemotherapy
Bevacizumab (Avastin): humanized IgG1 anti-VEGF moAb

**EARLY EFFECTS**

1. Regression of existing tumour microvasculature
2. Normalisation of remaining tumour vasculature

**CONTINUED EFFECTS**

3. Inhibition of new tumour vasculature

• Possible mechanisms of action
  – regression of existing microvasculature
  – normalisation of mature vasculature
  – inhibition of vasculature (re)growth
Bevacizumab: Phase II Studies with Chemotherapy

- Cytotoxic chemotherapy
  - Fluoropyrimidine + Platinum
  - CPT-11 + Platinum
  - Docetaxel + Platinum
  - Docetaxel + CPT-11 + Platinum
  - Docetaxel + 5-FU (LV) + Platinum
Bevacizumab: Phase II Study with CPT-11 + Cisplatin

- Regimen (every 3 weeks)
  - CPT-11 65 mg/m² iv D1, 8
  - Cisplatin 30 mg/m² iv D1, 8
  - Bevacizumab 15 mg/m² iv D1

- 47 pts with GEJ or GC

- RR = 65%, Median TTP = 8.3 mo, OS = 12.3 mo

- 6% Perforations, 28% G3 hypertension, 25% G3/4 thromboembolism

Bevacizumab: Phase III Trial for 1st line AGC: AVAGAST

N=760
Locally Advanced or Metastatic Gastric Cancer (stomach or gastro-oesophageal junction)

Randomization

XP + Placebo (3-weekly) for 6 cycles

Follow up survival status 3 monthly

Disease Progression (PD)

XP + Bevacizumab (3-weekly) for 6 cycles

X + Placebo (3-weekly) Until PD

X + Bevacizumab (3-weekly) Until PD

Primary endpoint = Overall Survival

XP = Xeloda® 1000 mg/m² bid po D1-14+
cisplatin 80 mg/m² iv D1

Bevacizumab 7.5 mg/kg iv
Bevacizumab: Phase III Trial for 1\textsuperscript{st} line AGC: AVAGAST

- Final analysis has been done
- Primary endpoint was not met
- Detailed results will be presented in ASCO
Bevacizumab: Phase III Trial for Operable Esophagogastric Cancer: MAGIC-B

**Primary endpoint: Overall Survival**

R = randomization
ECX: epirubicin, cisplatin, capecitabine

Resectable, type 2 / 3 EGJ and gastric cancer

N=1,100
IMC-1121B: anti-VEGFR2 Ab

- Humanized IgG1 against VEGFR-2 (KDR)
- Potently blocks the binding of the VEGF ligand to VEGFR-2, inhibits VEGF-stimulated activation of both VEGFR-2 and p44/p42 MAP kinases, and neutralizes VEGF-induced mitogenesis of human endothelial cells.
IMC-1121B: Phase III Trial for 2\textsuperscript{nd} line AGC

- Met adenocarcinoma: gastric or GEJ
- Measurable disease
- Radiographic PD during or within 4 or 6 months of last dose of 1\textsuperscript{st} line or adjuvant therapy, respectively
- PD on platinum- and/or fluoropyrimidine-containing combination rx
- ECOG PS 0-1

**Primary Endpoint**
- OS

<table>
<thead>
<tr>
<th>n</th>
<th>615 (459 events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centers</td>
<td>250 sites in Europe, NA, SA, CA, Asia, Australia/ NZ</td>
</tr>
<tr>
<td>Assumptions</td>
<td>Median OS from 5 to 7 mo (HR 1.4); alpha = 0.05; Power = 90%</td>
</tr>
</tbody>
</table>

**Stratify:**
- Geography (NA/EU/AU/NZ vs SA/CA vs Asia)
- Weight loss (≥10% over 3 mo vs <10%)
- Location of primary (gastric vs GEJ)
Sunitinib: a multi-target TKI
Sunitinib: Phase II Trial of Monotherapy for 2\textsuperscript{nd} line AGC

- N = 78 with 1 prior chemotherapy, ECOG PS 0-1
- Treatment
  - Sunitinib 50 mg po qd, 4 weeks on 2 weeks off
  - Median 2 cycles
- Efficacy
  - 2 PRs (2.6%), 25 SDs (32.1%)
  - Median PFS: 2.3 mos, OS: 6.8 mos
- Toxicities (G $\geq$3)
  - Neutropenia 34.6%, thrombocytopenia 29.4%
  - Fatigue 10%, HFS 6.4%, anorexia 6.4%, hyperbilirubinemia 6.4%, abdominal pain 5.1%
  - Causes of discontinuation: PD 55, adverse events 11, death 8, consent withdrawal 2

Bang, et al. Inv New Drug 2010
Studies of Sunitinib in Combination with Chemotherapy

- FOLFIRI
- FP
- XELOX
Sorafenib: a multi-target TKI

Tumor Cell

Endothelial Cell or Pericyte

HGF = hepatocyte growth factor

Sorafenib: Phase I-II Trial with cytotoxic chemotherapy for AGC

- Docetaxel + cisplatin
- Capecitabine + cisplatin
- S-1 + cisplatin
Sorafenib: Phase I Trial with Capecitabine + Cisplatin for 1\textsuperscript{st} line AGC

- **Recommended Dose Schedule (3 week cycle)**
  - Sorafenib 400 mg bid po \text{D1-21}
  - Capecitabine 800 mg/m\textsuperscript{2} bid po \text{D1}
  - Cisplatin 60 mg/m\textsuperscript{2} iv \text{D1}

- **N = 21**
- **RR (N=16)= 62.5%**
- **mPFS = 10 mo, mOS = 14.7 mo**
- **G3/4 toxicities**
  - Neutropenia 67%, 1 with fever
  - 1 perforation, HFS 14%

Kim, et al. 2009 ASCO
PI3K / AKT / mTOR Signaling

Funda Meric-Bernstam, JCO 2009
RAD001 (Afinitor): Phase II Trial for 2\textsuperscript{nd} or 3\textsuperscript{rd} line AGC

- RAD001 10 mg po daily
- N=53 previously treated with 1 (51%) or 2 (49%) chemotherapy regimen, but PS=0-1
- RR=0%, DCR=56%
- mPFS=2.7 mo, mOS=10.1 mo
- G3-4 toxicities: anemia (11%), hyponatremia (9.4%), increased GGT(7.5%), lymphopenia(7.5%)
- G1-2 pneumonitis in 15%

RAD001: Phase III Trial for 2nd or 3rd line AGC: GRANITE-1

Total number of patients needed: 663
All patients will have samples drawn for PK and biomarker assessments.
Response according to RECIST for response will be assessed every 6 weeks (see Post-Text Supplement 1).
Follow-up for overall survival will continue until the patient dies or is lost-to-follow (regardless of additional therapies after study participation)
* CoL questionnaires will be completed for all patients until disease progression is seen
RAD001: Phase II Trials with Chemotherapy for 1st line AGC

- HDFL + cisplatin
- MMC
- XELOX
Conclusions

- ToGA study has opened a new era of targeted therapy in the treatment of AGC.
- Many targeted agents proven effective in other solid tumors are now being developed in phase III trials in gastric cancer, mostly in combination with cytotoxic chemotherapy.
- Discovery of biomarkers predicting the efficacy of targeted agents are emphasized in gastric cancer as well as in other tumors.
- Participation in global clinical trials are highly recommended to facilitate the development of these promising treatments in gastric cancer.
Thank you!