New Agents in Gastric Cancer

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CONFLICT OF INTEREST DISCLOSURE

Employment: None; Stock Ownership: None

Consultant or Advisory Role: Merck Serono, Roche, Beigene, Bayer, Servier, Lilly, Novartis, Takeda, Astelas.

Research Funding: Genentech, Merck Serono, Roche, Beigene, Bayer, Servier, Lilly, Novartis, Takeda, Astelas, Fibrogen, Amcure, Sierra Oncology, Astra Zeneca, Medimmune, BMS, MSD

Speaking: Merck Serono, Roche, Angem, Bayer, Servier, Foundation Medicine.
Grant support: Merck Serono, Roche.

Others: Executive Board member of ESMO, Chair of Education ESMO, General and Scientific Director INCLIVA, Associate Editor: Annals of Oncology and ESMO Open, Editor in chief: Cancer Treatment Reviews.
Comprehensive molecular characterization of gastric adenocarcinoma

Molecular Characteristics of Chromosome instability subtype: Receptor Tyrosine Kinase Activation

# PHASE III TRIALS WITH TARGETED THERAPIES IN FIRST-LINE TREATMENT

For advanced gastroesophageal adenocarcinomas

<table>
<thead>
<tr>
<th>Trial</th>
<th>Chemotherapy</th>
<th>Biological</th>
<th>HR OS</th>
<th>P value</th>
<th>Increase in median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>ToGA(^1)</td>
<td>Cisplatin+5-FU/ capecitabine</td>
<td>Trastuzumab</td>
<td>0.74</td>
<td>0.04</td>
<td>+2.8 months</td>
</tr>
<tr>
<td>AVAGAST(^2)</td>
<td>Cisplatin+ capecitabine</td>
<td>Bevacizumab</td>
<td>0.87</td>
<td>0.10</td>
<td>+2.0 months</td>
</tr>
<tr>
<td>AVATAR(^3)</td>
<td>Cisplatin+ capecitabine</td>
<td>Bevacizumab</td>
<td>1.11</td>
<td>0.55</td>
<td>-0.9 months</td>
</tr>
<tr>
<td>RAINFALL(^4)</td>
<td>Cisplatin+5-FU/ capecitabine</td>
<td>Ramucirumab</td>
<td>0.96</td>
<td>0.68</td>
<td>0.5 month</td>
</tr>
<tr>
<td>EXPAND(^5)</td>
<td>Cisplatin+ capecitabine</td>
<td>Cetuximab</td>
<td>1.00</td>
<td>0.95</td>
<td>-1.3 months</td>
</tr>
<tr>
<td>REAL-3(^6)</td>
<td>Oxaliplatin+ epi- + capecitabine</td>
<td>Panitumumab</td>
<td>1.37</td>
<td>0.013</td>
<td>-2.5 months</td>
</tr>
<tr>
<td>RILOMET-1(^7)</td>
<td>Cisplatin+epi+ capecitabine</td>
<td>Rilotumumab</td>
<td>--</td>
<td>--</td>
<td>Stopped in futility analysis</td>
</tr>
<tr>
<td>METGASTRIC(^8)</td>
<td>FOLFOX6</td>
<td>Onartuzumab</td>
<td>1.06</td>
<td>0.83</td>
<td>-0.6 months</td>
</tr>
</tbody>
</table>

Tumor Heterogeneity as the main limitation for targeted agents in GEA

FGFR molecular alterations in Gastric Cancer

FGFR2b overexpression or FGFR2 amplification is associated with a poor prognosis


Figure 2 Representative images of FGFR2b expression interpreted by immunohistochemistry as 3+ (a), 2+ (b), and 1+ (c). Immunohistochemistry results correlated well with copy numbers obtained by FISH. Samples designated as 3+, 2+, and 1+ show high amplification (d), moderate amplification (e), and mild copy number gain (f), respectively.
FGFR molecular alterations in Gastroesophageal Adenocarcinomas

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>FGFR2 WT (n = 6,398)</th>
<th>FGFR2 SV (n = 40)</th>
<th>p value</th>
<th>FGFR2 amp (n = 209)</th>
<th>p value</th>
<th>FGFR2 RE (n = 37)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:Female</td>
<td>2.8:1</td>
<td>1.2:1</td>
<td>.01</td>
<td>1.6:1</td>
<td>.0003</td>
<td>1.6:1</td>
<td>.14</td>
</tr>
<tr>
<td>Median age, years</td>
<td>62</td>
<td>64</td>
<td>.34</td>
<td>59</td>
<td>.04</td>
<td>62</td>
<td>.88</td>
</tr>
<tr>
<td>TMB, median</td>
<td>4.35</td>
<td>4.78</td>
<td>.49</td>
<td>3.60</td>
<td>.79</td>
<td>3.48</td>
<td>.41</td>
</tr>
<tr>
<td>TMB, mean</td>
<td>6.06</td>
<td>11.1</td>
<td>.06</td>
<td>4.49</td>
<td>.17</td>
<td>4.28</td>
<td>.52</td>
</tr>
<tr>
<td>% MSI-H</td>
<td>3.07%</td>
<td>16.22%</td>
<td>.0009</td>
<td>0.00%</td>
<td>.01</td>
<td>0.00%</td>
<td>.99</td>
</tr>
<tr>
<td>RTK amp</td>
<td>24.0%</td>
<td>10%</td>
<td>.04</td>
<td>13.9%</td>
<td>.0005</td>
<td>24.3%</td>
<td>.99</td>
</tr>
<tr>
<td>ERRB2 amp</td>
<td>14.7%</td>
<td>7.5%</td>
<td>.26</td>
<td>6.70%</td>
<td>.0006</td>
<td>13.5%</td>
<td>.99</td>
</tr>
<tr>
<td>EGFR amp</td>
<td>6.51%</td>
<td>2.5%</td>
<td>.52</td>
<td>7.66%</td>
<td>.48</td>
<td>10.8%</td>
<td>.30</td>
</tr>
<tr>
<td>MET amp</td>
<td>4.61%</td>
<td>0%</td>
<td>.26</td>
<td>2.87%</td>
<td>.31</td>
<td>5.41%</td>
<td>.69</td>
</tr>
<tr>
<td>Multiple FGFR2</td>
<td>0%</td>
<td>10%</td>
<td>NP</td>
<td>7.66%</td>
<td>NP</td>
<td>37.8%</td>
<td>NP</td>
</tr>
</tbody>
</table>

Bolded p values are statistically significant (p < .05). All p values are based off comparison with FGFR2 WT.

Abbreviations: amp, amplification; EGFR, epidermal growth factor receptor; FGFR2, fibroblast growth factor receptor 2; MSI-H, microsatellite instability-high; NP, not performed; RE, rearrangement; SV, short variant; TMB, tumor mutational burden; WT, wild type.
FGFR inhibitors in Clinical trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase</th>
<th>Clinical trials. gov</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multikinase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dovitinib</td>
<td>Phase II</td>
<td>NCT01379534</td>
<td>FGFR2-mutant or wild-type endometrial cancer</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td>NCT01732107</td>
<td>FGFR3-mutant or overexpressed BCG refractory urothelial carcinoma</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td>NCT01719549</td>
<td>FGFR2-amplified gastric cancer</td>
</tr>
<tr>
<td>Lucitanib</td>
<td>Phase I/II</td>
<td>NCT01283945</td>
<td>Expansion cohort in FGFR1-amplified tumors</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>Phase II/III</td>
<td>NCT01761747</td>
<td>Advanced squamous cell lung cancers with FGFR kinase alterations</td>
</tr>
<tr>
<td><strong>Selective FGFR inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZD4547</td>
<td>Phase I</td>
<td>NCT00979134</td>
<td>Expansion cohort in FGFR1- or FGFR2 amplified tumors</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td>NCT01457846</td>
<td>Gastric or lower-esophageal cancer, FGFR2-amplified or not, randomized to AZD4547 or paclitaxel</td>
</tr>
<tr>
<td></td>
<td>Phase I/II</td>
<td>NCT01202591</td>
<td>Estrogen receptor + and FGFR1-amplified breast cancer, randomized to AZD4547 plus fulvestrant or fulvestrant alone</td>
</tr>
<tr>
<td>BGJ398</td>
<td>Phase I</td>
<td>NCT01004224</td>
<td>FGFR1- or FGFR2-amplified, FGFR3-mutant advanced cancer</td>
</tr>
<tr>
<td>LY2874455</td>
<td>Phase I</td>
<td>NCT01212107</td>
<td>Advanced cancer with FGFR aberrations during dose expansion</td>
</tr>
<tr>
<td>JNJ-42756493</td>
<td>Phase I</td>
<td>NCT01703481</td>
<td>Expansion cohort in FGFR1-, FGFR2-, or FGFR4-amplified tumors</td>
</tr>
</tbody>
</table>

AZD4547, a selective FGFR-1, 2, 3 TKI vs Paclitaxel in advanced gastric carcinoma with FGFR polysomy or gene amplification in a Randomized phase II trial

AZD4547, a selective FGFR-1, 2, 3 TKI vs Paclitaxel in advanced gastric carcinoma with FGFR polysomy or gene amplification in a Randomized phase II trial

AZD4547, a selective FGFR-1, 2, 3 TKI vs Paclitaxel in advanced gastric carcinoma with FGFR polysomy or gene amplification in a Randomized phase II trial

• First-in-class humanized monoclonal IgG1 antibody that selectively blocks FGFR2b and triggers antibody-dependent cell-mediated cytotoxicity.

• With favorable safety and activity as a single agent in 2L+ patients with FGFR2b+ GC.

Bemarituzumab: The phase I-III FIGHT Trial

Box 2. FIGHT study end points.

Cohort 2
FPA144 15 mg/kg Q2W with one dose of 75 mg/kg on Day 8 of Cycle 1 only + mFOLFOX6

Cohort 1a (if needed)
FPA144 15 mg/kg Q2W + mFOLFOX6

FPA144 Recommended dose from Phase 1
Randomization

Cohort 1b (if needed)
FPA144 intermediate dose + mFOLFOX

FPA144 + mFOLFOX6
Placebo + mFOLFOX6

Phase 1 open label, dose escalation
Advanced gastrointestinal cancer (GI)

Phase 3 double blind, randomized controlled
FGFR2+-selected advanced gastric or gastroesophageal cancer (GC)

Primary end point
- Overall survival

Secondary end points
- PFS
- ORR
- Safety and tolerability
- Pharmacokinetic parameters in
- Incidence of treatment-emergent anti-FPA144 antibody response

DOR: Duration of response; ORR: Objective response rate; PFS: Progression-free survival; RECIST: Response evaluation criteria in solid tumors.

RAS Amplified Gastric Cancers

Targeting wild-type KRAS-amplified gastroesophageal cancer through combined MEK and SHP2 inhibition

## PHASE III TRIALS ON HER2 BLOCKADE
For HER2 amplified advanced gastroesophageal adenocarcinomas

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>Chemotherapy backbone</th>
<th>Line of therapy number</th>
<th>HR</th>
<th>P value</th>
<th>Response rate</th>
<th>Increase in median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>ToGA¹</td>
<td>Cisplatin+5-FU/capcitabine</td>
<td>First 584</td>
<td>0.74</td>
<td>0.04</td>
<td>51% vs. 37% p=0.0017</td>
<td>+2.8 months</td>
</tr>
<tr>
<td>LOGiC²</td>
<td>Oxaliplatin/capcitabine +/-Lapatinib</td>
<td>First 545</td>
<td>0.91</td>
<td>0.35</td>
<td>53% vs. 39% p=0.031</td>
<td>+1.7 months</td>
</tr>
<tr>
<td>TyTAN³</td>
<td>Paclitaxel+/-Lapatinib</td>
<td>Second 261</td>
<td>0.84</td>
<td>0.20</td>
<td>27% vs. 9% p=0.001</td>
<td>+2.1 months</td>
</tr>
<tr>
<td>GATSBY⁴</td>
<td>TDM-1 vs Taxane</td>
<td>Second 345</td>
<td>1.15</td>
<td>0.85</td>
<td>NP</td>
<td>- 0.7 months</td>
</tr>
<tr>
<td>JACOB⁵</td>
<td>Cisplatin+5-FU/cap/Trastu +/- Pertuzumab</td>
<td>First 780</td>
<td>0.84</td>
<td>0.056</td>
<td>56% vs. 48% P=0.026</td>
<td>3.3 months</td>
</tr>
</tbody>
</table>

New drugs under development for HER2 amplified GEA

Trastuzumab Deruxtecan (DS8021a) a novel HER2-targeted antibody–drug conjugate in HER2 amplified GEA

Trastuzumab deruxtecan in HER2 amplified GC after Trastuzumab progression

Confirmed Response Rate 43.2%

Median PFS 5.6 months

Figure 2: Progression-free survival for trastuzumab deruxtecan 5.4 mg/kg or 6.4 mg/kg in patients with HER2-positive gastric or gastro-oesophageal junction cancer. Progression-free survival is based on investigator assessment. Vertical tick marks indicate where data was censored.

Figure 3: Best percentage change in tumour size from baseline in individual patients with gastric or gastro-oesophageal junction cancer treated with trastuzumab deruxtecan (5.4 mg/kg or 6.4 mg/kg doses; n=44). Dotted lines denote 20% increase or 30% reduction in tumour size.

New drugs under development for HER2 amplified GEA

MCLA 128 a bispecific HER2-Her3 antibody after Trastuzumab progression

• In a phase I/II trial, common related AEs were infusion-related reactions (19%), diarrhea (17%), asthenia/fatigue (15%), nausea (6%), and decreased appetite (5%). Four (4%) pts had suspected related grade 3-4 AEs. No clinically significant LVEF decline was seen.

• MCLA-128 is very well tolerated with mainly grade 1/2 AEs.

• Promising single agent antitumor activity was seen in heavily pretreated GC/GEJ pts progressing on anti-HER2 therapy. Further clinical exploration of MCLA-128 in GC/GEJ pts is warranted.
DNA repair inhibitors: Fluzoparib and Pamiparib

Fluzoparib is an oral, selective PARP1 inhibitor. In gastric cancer PDX model, fluzoparib + apatinib + paclitaxel demonstrated significant tumor growth inhibition as compared to apatinib alone, and fluzoparib + paclitaxel. The combination was tested in a phase I trial to identify the RP2D.

Pamiparib is a selective PARP1/2 inhibitor that crosses the blood-brain barrier, has shown potent DNA–PARP trapping, and has demonstrated antitumor activity in preclinical models. In early phase clinical studies, was well tolerated and showed preliminary antitumor activity. Actually an on going randomised phase III trial is on going with pamiparib as maintenance treatment.
**Clauvin18.2**

- Member of the claudin family
- Major structural component of tight junctions
- Seals intercellular space in epithelial sheets
- Not expressed in any healthy tissues, except: stomach mucosa, but with limited accessibility

### Immunohistological CLDN18.2 Labeling

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Total</th>
<th>Total</th>
<th>Any positivity</th>
<th>CLDN18.2 [≥2+ &gt;40%]</th>
<th>CLDN18.2 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric adenocarcinomas</td>
<td>1205</td>
<td>977</td>
<td>81</td>
<td>603</td>
<td>50</td>
</tr>
<tr>
<td>Diffuse</td>
<td>358</td>
<td>320</td>
<td>89</td>
<td>216</td>
<td>60</td>
</tr>
<tr>
<td>Intestinal</td>
<td>395</td>
<td>287</td>
<td>73</td>
<td>168</td>
<td>43</td>
</tr>
<tr>
<td>Mixed</td>
<td>64</td>
<td>49</td>
<td>77</td>
<td>30</td>
<td>47</td>
</tr>
<tr>
<td>Not specified</td>
<td>388</td>
<td>321</td>
<td>83</td>
<td>189</td>
<td>49</td>
</tr>
</tbody>
</table>

Lordick F et al. *ESMO Asia* 2016; #2200
A multicentre, phase 2a study of zolbetuximab as a single agent in patients with recurrent or refractory advanced adenocarcinoma of the stomach or lower oesophagus: the MONO study
FAST - Patient Distribution

- Centers in GER (10), CZE (2), LAT (3), RUS (18), UKR (12),

Consented for CLDN18.2 screen: N = 730

CLDN18.2 assessable: N = 686

pts Randomized: N = 252

pts Treated: N = 246

- Arm 1
  - EOX
  - N = 84

- Arm 2
  - EOX/IMAB362
  - 800/800 mg/m²
  - N = 77

- Arm 3
  - EOX/IMAB362
  - 1000 mg/m²
  - N = 85

Excluded (n = 478)

- 44 pts w/o tumor tissue sample
- 352 pts CLDN18.2 neg/low expressors
- 82 pts eligibility criteria not fulfilled (19 WoC, 63 others)

Not treated (n = 6)

- 1 pt in Arm 1 (Anemia G2)
- 2 pts in Arm 2 (SAE/Anemia G3, WoC)
- 3 pts in Arm 3 (AE/incre. liver enzymes, SAE/deep vein thrombosis, WoC)

Safety Set = Full Analysis Set
(Pts with ≥ 1 treatment of any study drug)

Al-Batran SE, et al. ASCO 2016 (LBA4001)
Zolbetuximab Claudin 18.2 inhibition: FAST TRIAL

Presented By Salah-Eddin Al-Batran at 2016 ASCO Annual Meeting
Thank you