GASTRIC CANCER: Update on Novel Agents

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Novel Agents in Gastric Cancer

- Conventional Chemo
- Novel cytotoxic agents
- Angiogenesis inhibitors
- DNA Damage repair
- Genomics and Targets
- Novel Monoclonal antibodies
FLO vs FLOT: Patients 65 and older

- 143 patients, median age of 70
- FLO: Ox, LV, FU CIV over 24 hours every 2 weeks vs
- FLOT: + Docetaxel 50 mg/m2
- RR: 49% vs 28% p = 0.016, FLOT better
- PFS: 9 vs 7 months p = 0.079  OS: 17.3 vs 14.5 months p = 0.39, FLOT not better
- Toxicity: greater with FLOT (82% vs 39% grade 3/4 AE’s)

Al Batran EJC 49: 835-842; 2013
FLO = FLOT: Patients 65 and older

PFS Local Disease

PFS Met Disease

OS

Al Batran EJC 49: 835-842; 2013
Abstract #4009: Phase III study comparing triplet chemotherapy with S-1 and cisplatin plus docetaxel versus doublet chemotherapy with S-1 and cisplatin for advanced gastric cancer (JCOG1013)


Stomach Cancer Study Group of Japan Clinical Oncology Group (JCOG), Japan
Primary Endpoint: Overall survival (OS)

<table>
<thead>
<tr>
<th></th>
<th>CS</th>
<th>DCS</th>
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</thead>
<tbody>
<tr>
<td>1-year OS (95% CI)</td>
<td>61.5%</td>
<td>59.7%</td>
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<tr>
<td>Median OS (95% CI)</td>
<td>15.3 m</td>
<td>14.2 m</td>
</tr>
<tr>
<td>HR (95% CI) p value (1-sided)</td>
<td>0.99 (95% CI 0.85-1.16)</td>
<td>0.47</td>
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<tr>
<td>ORR</td>
<td>56.0%</td>
<td>59.3%</td>
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</table>
Key Secondary Endpoint: OS according to histological type

Intestinal type (n=259)

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<tr>
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<tbody>
<tr>
<td>Median OS (95% CI)</td>
<td>17.5 m (15.0-20.6)</td>
<td>17.5 m (14.0-20.4)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.06 (0.81-1.39)</td>
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</table>

Diffuse type (n=482)

<table>
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<tr>
<th></th>
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<th>DCS</th>
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<tbody>
<tr>
<td>Median OS (95% CI)</td>
<td>14.2 m (12.2-15.6)</td>
<td>13.3 m (11.7-14.5)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.98 (0.81-1.18)</td>
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</table>

Overall survival was significantly shorter in the diffuse type (median, 13.7 months, 95% CI 12.5-14.6) than in the intestinal type (17.5 months, 15.7-18.9; HR 1.38, 95% CI 1.17-1.62).
Novel Cytotoxics

- **DREAM**: Oral Taxane DHP107 vs Paclitaxel
  - 236 pts failing first line therapy
  - PFS DHP 3.0 mo = Pac 2.6 mos: “noninferior”
  - OS DHP 9.7 mos = Pac 8.9 months
  - RR 17.8% vs 25.4%.
  - Equal rates of neutropenia, nadir fever
  - More GI toxicity for DHP

- **TAS 102 vs BSC 3rd or later line**
  - Trifluridine + Tipiracil
  - Primary endpoint of improved OS was met
  - Will become a salvage late line option

- **TAS 118**: S-1 + Leucovorin
  - Phase III SOLAR: TAS118 + Oxaliplatin vs S-1 + Cisplatin (NCT02322593)

*Kang Ann Oncol 29: 1220; 2018, Tabernero GI ESMO 2018*
## Recent phase 3 of new agents for GC

<table>
<thead>
<tr>
<th>Target</th>
<th>Trial/Author</th>
<th>Line</th>
<th>Screening</th>
<th>Agent</th>
<th>control</th>
<th>Endpoint</th>
<th>Results</th>
<th>difference mOS (HR)</th>
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<tbody>
<tr>
<td>HER2</td>
<td>ToGA</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>HER2</td>
<td>Trastuzumab</td>
<td>(+chemo)</td>
<td>OS</td>
<td>Positive</td>
<td>+2.7 (HR 0.74)</td>
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<tr>
<td>HER2</td>
<td>Logic</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>HER2(FISH)</td>
<td>Lapatinib</td>
<td>PBO (+chemo)</td>
<td>OS</td>
<td>Negative</td>
<td>+1.7 (HR 0.91)</td>
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<tr>
<td>HER2</td>
<td>JACOB</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>HER2</td>
<td>Pertuzumab</td>
<td>PBO (+Chemo+T)</td>
<td>OS</td>
<td>Negative</td>
<td>+3.3 (0.84)</td>
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<tr>
<td>HER2</td>
<td>TyTAN</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>HER2(FISH)</td>
<td>Lapatinib</td>
<td>(+chemo)</td>
<td>OS</td>
<td>Negative</td>
<td>+3 (HR 0.84)</td>
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<tr>
<td>HER2</td>
<td>GATSBY</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>HER2</td>
<td>T-DM1</td>
<td>Taxanes</td>
<td>OS</td>
<td>Negative</td>
<td>-0.7 (HR 1.15)</td>
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<tr>
<td>EGFR</td>
<td>REAL-3</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>-</td>
<td>Panitumumab</td>
<td>(+chemo)</td>
<td>OS</td>
<td>Negative</td>
<td>-2.5 (HR 1.37)</td>
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<tr>
<td>EGFR</td>
<td>EXPAND</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>-</td>
<td>Cetuximab</td>
<td>PBO (+chemo)</td>
<td>PFS</td>
<td>Negative</td>
<td>-1.3 (HR 1.0)</td>
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<td>EGFR</td>
<td>ENRICH</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>EGFR(IHC)</td>
<td>Nimotuzumab</td>
<td>(+chemo)</td>
<td>OS</td>
<td>Negative</td>
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<td>mTOR</td>
<td>GRANITE-1</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;/3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>-</td>
<td>Everolimus</td>
<td>PBO</td>
<td>OS</td>
<td>Negative</td>
<td>+1.05 (HR 0.9)</td>
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<td>mTOR</td>
<td>GRANITE-2</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>-</td>
<td>Everolimus</td>
<td>PBO (+chemo)</td>
<td>OS</td>
<td>Negative</td>
<td>+1.0 (HR 0.92)</td>
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<td>HGF</td>
<td>RILOMET1</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>MET(IHC)</td>
<td>Rilotumumab</td>
<td>PBO (+chemo)</td>
<td>OS</td>
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<td>-2.9 (HR 1.36)</td>
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<td>MET</td>
<td>METgastric</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>MET(IHC)</td>
<td>Onartuzumab</td>
<td>PBO (+chemo)</td>
<td>OS</td>
<td>Negative</td>
<td>-0.3 (HR 0.82)</td>
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<td>VEGF-A</td>
<td>AVAGAST</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>-</td>
<td>Bevacizumab</td>
<td>PBO (+chemo)</td>
<td>OS</td>
<td>Negative</td>
<td>+2 (HR 0.87)</td>
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<tr>
<td>VEGFR2</td>
<td>RAINFALL</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>-</td>
<td>Ramucirumab</td>
<td>PBO (+chemo)</td>
<td>OS</td>
<td>Negative</td>
<td>+0.4 (HR 0.96)</td>
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<tr>
<td>VEGFR2</td>
<td>REGARD</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>-</td>
<td>Ramucirumab</td>
<td>PBO</td>
<td>OS</td>
<td>Positive</td>
<td>+1.4 (HR 0.776)</td>
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<tr>
<td>VEGFR2</td>
<td>RAINBOW</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>-</td>
<td>Ramucirumab</td>
<td>PBO (+chemo)</td>
<td>OS</td>
<td>Positive</td>
<td>+2.2 (HR 0.807)</td>
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<tr>
<td>VEGFR2</td>
<td>Li, et al</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>-</td>
<td>Apatinib</td>
<td>PBO</td>
<td>OS</td>
<td>Positive</td>
<td>+1.8 (HR 0.71)</td>
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<tr>
<td>PARP</td>
<td>GOLD</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>ATM(IHC)</td>
<td>Olaparib</td>
<td>PBO (+chemo)</td>
<td>OS</td>
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<td>+1.9 (HR 0.79)</td>
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<td>STAT3</td>
<td>BRIGHTER</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>-</td>
<td>Napabucasin</td>
<td>PBO(+chemo)</td>
<td>OS</td>
<td>Negative</td>
<td>+0.3 (HR 1.01)</td>
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<tr>
<td>PD1</td>
<td>Keynote061</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>PDL1 (IHC)</td>
<td>Pembrolizumab</td>
<td>Paclitaxel</td>
<td>OS</td>
<td>Negative</td>
<td>+0.8 (HR 0.82)</td>
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<tr>
<td>PD1</td>
<td>JAVELIN300</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>-</td>
<td>Avelumab</td>
<td>Iri/taxanes/BSC</td>
<td>OS</td>
<td>Negative</td>
<td></td>
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<tr>
<td>PD1</td>
<td>ATTRACTION-2</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt;-</td>
<td>-</td>
<td>Nivolumab</td>
<td>PBO</td>
<td>OS</td>
<td>Positive</td>
<td>+1.2 (HR 0.63)</td>
</tr>
</tbody>
</table>

Only 5 / 22 positive trials
Difference in median survival: 1.2~2.7ms (vs. placebo)

Presented By Kohei Shitara at 2018 ASCO Annual Meeting
Angiogenesis Agents

- Ramucirumab: VEGFR2
- Second line: RAM vs BSC: Improved OS, PFS
  - REGARD
- Second Line: Pac/RAM vs Pac: Improved OS, PFS, RR
  - RAINBOW
- First line: Cape/Cis/RAM vs Cape/Cis: failed to improve OS, RR, despite improvement in PFS
  - RAINFALL

Angiogenesis Agents

- Paclitaxel + Ramucirumab is standard second line therapy and key partner for second line new drug development
- Ram: may modulate tumor microenvironment and impact on Tregs
- Ram: may modulate impact of DNA damaging agents
- Trials of including Ram + / - Pac with checkpoint inhibitors, PARP inhibitors, and other agents in early phase development
Angiogenesis Agents: TKIs

- **Apatinib**: VEGFR TKI, third or later line vs BSC
  - China: 267 pts, Improved OS vs BSC: 6.5 mos vs 4.7 mos (HR 0.709)
  - West: phase 3 vs BSC [NCT03042611]

- **Regorafenib**: VEGFR and multitargeted TKI, second or later line
  - Phase II vs BSC: PFS 2.6 vs 0.9 mos, OS trended better
  - Phase 3 vs BSC (NCT02773524)

- **TKI + anti PD-1 and PDL-1**
  
  Li JCO 34: 1448; 2016; Pavlakis JCO 43: 2728; 2016
DNA Damaging Agents: PARP Inhibition

- Paclitaxel + / - Olaparib, Phase II
  - Improvement in OS, ATM negative pts

- GOLD: phase III
  - 525 eligible pts: Paclitaxel + / - Olaparib 100 mg BID
  - 94 ATM negative also randomized

- No difference OS + olaparib
  - 8.8 vs 6.9 mos (HR 0.79)
  - ATM negative: 12 vs 10 mos (HR 0.73)

- Δ 5 mos, underdosing, p53 status

- PARP + Ram+ / -Pac, PD-1, PDL-1

Bang Lancet Oncol 18: 1637, 2017
Targeting Stem Cell Pathways

- **BBI608: Napabucasin**
  - Small molecule that inhibits STAT3, B-catenin, NANG
  - May inhibit “stemness”

- **Phase III: Brighter**
  - Paclitaxel + / - BBI608
  - 700 patients, unblinded after 380 events for futility
  - No difference in PFS, OS

- **B-catenin**
  - Activation may reduce T cell infiltration
  - Targeting with BBI6068 + PD-1, PDL-1 agents

Shah J Clin Oncol 36: 2018 (suppl, Abst 4010)
**OS, PFS, DCR, and Objective Response Rates**

**Outcome Variable** | **Napabucasin+Paclitaxel (n=357)** | **Placebo+Paclitaxel (n=350)** | **P-value**
--- | --- | --- | ---
Disease control rate, % (95% CI) | 55 (49, 61) | 58 (52, 64) | 0.6555
Objective response rate, % (95% CI) | 16 (12, 21) | 18 (14, 23) | 0.7358

Presented By Joseph Chao at 2018 ASCO Annual Meeting
TCGA: Gene Amplification in Esophagogastric Cancer

296 Esophageal / Gastric Cancers, 190 CRC

- Amplified genes in 37% Gas / Eso tumors
  - EGFR
  - HER2
  - MET
  - FGFR1-2
  - KRAS

- Targetable Receptors and Receptor Tyrosine Kinases

296 Esophageal / Gastric Cancers, 190 CRC

- Amplified genes in 37% Gas / Eso tumors
  - EGFR: failed
  - HER2: mixed
  - MET: failed
  - FGFR1-2: ongoing
  - KRAS

- Targetable Receptors and Receptor Tyrosine Kinases

Four Genomic Subsets: Therapeutic Implications of TCGA

- **Genomically unstable**
  - RTK directed therapy: HER2 only success

- **MSI**
  - Immune checkpoint inhibitors: approved for refractory MSI high solid tumors

- **Genomically stable**
  - Not clearly targetable

- **Epstein-Barr virus**
  - PIK3CA, immune checkpoint inhibitors

Nature 24: 2903; 2014
HER2 Targeted Agents: Esophagogastric Cancer is not Breast Cancer

- Trastuzumab has modest first line activity
  - TOGA: Cape-Cis + trastuzumab improved RR, PFS, OS

- First Line Lapatinib (LOGIC) + Cape / Oxaliplatin
  - No difference in OS
  - 12.2 vs 10.5 mos (HR 0.91)

- Pertuzumab (JACOB) failed to improve OS + Trastuzumab / Cisplatin / FP
  - 780 pts
  - OS 17.5 vs 14.2 mos (HR 0.84, p - 0.056)

HER2 Targeted Agents: Second Line

- Second line: trastuzumab emtansine (TDM-1) no better than a taxane in 345 pts (OS 7.9 vs 8.6 mos, HR 1.15)

- T-ACT: phase II
  - 90 pts POD first line Trastuzumab
  - Paclitaxel + / - Trastuzumab
  - PFS primary endpoint
  - No difference PFS, OS

- De novo and acquired HER2 resistance are likely

HER2 Resistance: Up Front

- Bass lab TCGA
- 42 HER2 amplified untreated primary tumors
- 55% had concurrent other genomic event
  - Cell cycle: 41%
    - Cyclin dependent kinase CCNE1 amplified in 24%
  - PI3K: 12% (PI3K, PTEN, AKT)
  - RTK: 14% (HER-3, MET, FGFR2)
- Targetable pathways to overcome resistance
  
  Kim et al J Clin Invest 124: 5145; 2014
HER2 Resistance: Acquired

- MSK: NGS IMPACT
- 44 pts post Trastuzumab, 23 matched pre / post pairs
- At progression
  - 7/44 (16%) lost HER-2 expression (FISH and IHC)
  - Increase amplification/mutation in EGFR, ERBB4, IGF1R, MET
  - Increase amplification or mutation of SMAD4, KRAS, PIK3CA, PTEN, MTOR

Janjigian Cancer Discovery 2017
HER2 Resistance: Acquired

- 23 pre/post trastuzumab paired samples
- Abnormalities post trastuzumab most common SMAD4, MET, KRAS, CDKN2A, ERBB4, IGF1R

Janjigian Cancer Discovery 2017
Phase III Trials: EGFr

- Trials conducted with no biomarker selection of patients
- **REAL 3**: ECX + / - Panitumumab (U.K.)
  - Negative: Panitumumab had inferior outcomes
- **EXPAND**: Cape-Cis + / Cetuximab (E.U.)
  - Negative: Cetuximab trended inferior
- **Nimotuzumab**: Phase II Irinotecan + / - N second line
  - PFS 75 vs 83 days, OS 250 vs 232 days
- **COG**: BSC vs Gefitinib (U.K.): Negative
  - EGFR amplification or copy number a predictive biomarker

Other Phase II → III Disappointments in Gastric Ca

MET Receptor Inhibitors

RILOMET-1: OS
Experimental: 9.6mo
Control Arm: 11.5mo
HR 1.37; p = 0.016

MetGastric: OS ITT
Experimental: 11.0mo
Control Arm: 11.3mo

MetGastric: OS MET2+/3+
Experimental: 11.0mo
Control Arm: 9.7mo
HR 0.64; p = 0.062

Cunningham Lancet Oncol 18:1467; 2017, Shah JAMA Oncol 3: 620; 2017
**FGFR**

- **Biomarker selection**
  - Gene amplification or copy number
  - Gene rearrangement or fusion
  - Activating mutations

- **AZD4547; mixed results**
  - RTK inhibitor
  - 9 pts GE cancers with amplified FGFR1-2
  - 3 responses seen
  - Shine Trial: AZD4547 vs paclitaxel
    - 71 pts, PFS 1.8 vs 3.5 mos for Paclitaxel, 1.5 vs 2.3 in 9% FGFR amplified

- **Bemartuzumab: FGFR2, inhibits ligand binding and enhances ADCC**
  - 19% RR phase I in FGFR2 overexpressing gastric cancer
  - Phase III with FOLFOX (NCT03343301)  
  
  *Pearson Cancer Disc 6: 2016; Bang JCO 33: 2015*
CLDN18.2 IS EXPRESSED IN SEVERAL CANCER TYPES

- Member of the claudin family
- Major structural component of tight junctions
  - Seals intercellular space in epithelial sheets
- Not expressed in any healthy tissues, except for stomach mucosa, with limited accessibility to the antibody
- Broadly expressed in various cancer types
**FAST: RANDOMIZED OPEN-LABEL MULTICENTER PHASE 2 IN 1ST LINE GEC**

6/2012 FPI arms1&2

1:1

CLAUDETECT IVD TEST
2+/3+ in ≥40%

15/2013 FPI arm3

1:1:7

Arm 1 N=84 → EOX, max 8x

Arm 2 N=77 → EOX, max 8x → 800/600mg/m² IMAB362 q3w until PD → Arm 3 N=85 → EOX, max 8x → 1000mg/m² IMAB362 q3w until PD

- Randomized phase II trial with IMAB362 in combination with EOX.
- Arm 1, Arm 2 randomized 1:1
- Added exploratory Arm 3, 1:1:7 randomization for catch up
- At randomization: Stratification according to (i) CLDN18.2 positivity, (ii) measurability of disease

**Key inclusion criteria:**
- Gastric, esophageal or the gastroesophageal junction adenocarcinoma
- 1st line, no prior CTx for advanced disease
- Locally advanced, resections with R2 outcome, metastatic disease.
- CLDN18.2: 2+/3+ intensity in ≥40% tumor cells
- Measurable, non-measurable disease according to RECISTv1.1
- ECOG 0-1
- Adequate renal, cardiac, hematological, and hepatic function

**Key primary end point:** PFS

**Key secondary endpoint:** OS

**EOX:**
- Epirubicin, 50 mg/m², d1 of each cycle
- Oxaliplatin, 130 mg/m², d1 of each cycle
- Capecitabine, 1250 mg/m² per day, d1-21 of each cycle
FAST TRIAL EFFICACY DATA – ARM 2 VS ARM 1

OS in pts with 2+/3+ CLDN18.2 staining in ≥ 40% of tumor cells

- EOX (34)
- EOX + IMAB362 360/600 mg/m² (77)
- mOS 8.4 vs 13.2 months
- HR 0.51
- P=0.0001

Patient disposition
<table>
<thead>
<tr>
<th></th>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
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<tbody>
<tr>
<td>pts with event N (%)</td>
<td>75 (89.3)</td>
<td>53 (68.6)</td>
</tr>
<tr>
<td>OS [median (95% CI), months]</td>
<td>8.4 (7.0; 10.3)</td>
<td>13.2 (9.7; 18.9)</td>
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<tr>
<td>Rates</td>
<td>24w rate</td>
<td>70.9</td>
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<tr>
<td></td>
<td>60w rate</td>
<td>18.7</td>
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<tr>
<td>Hazard ratio</td>
<td></td>
<td>0.51</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td>(0.36; 0.73)</td>
</tr>
<tr>
<td>p-value (one-sided, stratified Cox model)</td>
<td>0.0001</td>
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</tbody>
</table>

► mOS improvement 4.8 months (8.4 vs 13.2) by adding 800/600 mg/m² IMAB362 to EOX
FAST - Overall Survival

Total Population*

- HR 0.51
- P=0.0001

- 13.2mo
- 8.4mo

High Expressors#

- HR 0.45
- p=<0.0005

- 16.7mo
- 9.0mo

* in patients with 2+/3+ CLDN18.2 staining in ≥ 40% of tumor cells

# in patients with 2+/3+ CLDN18.2 staining in ≥ 70% of tumor cells
MMP9

- GS-5745: moAb inhibitor of matrix metalloproteinase 9 (MMP9)
- Phase I + FOLFOX: in 30 chemo naïve PFS 12 mos RR 57%
- Phase III + FOLFOX FIGHT Trial (NCT03343301)
Bi Specific, Other Monoclonal Antibodies

- **Margetuximab: HER2**
  - Anti HER-2 with optimized Fc domain to increase activation of CD16A receptors on NK cells
  - Phase I / II + Pembrolizumab

- **DS-8201: HER2**
  - Trastuzumab conjugated to a topo-I inhibitor
  - 43% response in 23 pts
  - Randomized phase II vs paclitaxel or irinotecan (NCT NCT03384940)

- **CEA-TCB**
  - T cell bispecific targeting CD3, CEA
  - + Atezolizumab

Doi Lancet Oncol 11: 1512; 2017
Gastric Cancer: Novel Agent Update

- Two drug regimens preferred first line (JCOG1013)
- Novel Cytotoxics: TAS102 effective in refractory disease

Angiogenesis Agents
  - Ramucirumab + Paclitaxel: Backbone for second line therapy trials
    - + Immune Checkpoint, PARP inhibitors
  - Apatinib, Regorafenib TKIs in phase III trials, novel combinations

Genomics identifies targetable subpopulations
  - RTK amplification, MSI High

HER2: second line continuation of trastuzumab is not beneficial
  - Resistance due to HER2 loss, escape pathways (EGFR, MET)

FGFR inhibitors are in phase III

Matrix metalloproteinase inhibitors, IMAB362 targeting Claudin 18.2, are in phase III

Novel conjugate and bispecific antibodies