ADVANCED GASTRIC CANCER
Chemotherapy and anti-angiogenic Treatment

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University Hospital Leipzig, Germany

Barcelona, 30 August 2019
DISCLOSURE OF INTEREST

Florian Lordick


Leadership roles: ESMO (Director of Education Elect), EORTC (Chairman of the GI Tract Cancer Group), German Cancer Society (Secretary), International Gastric Cancer Association (President)
ADVANCED GASTRIC CANCER

Epidemiology

Age-standardised incidence of gastric cancer, 2018

- **Over 1 million** new cases in 2018
- **5th** most common malignancy
- **3rd** leading cause of cancer death

Between **40 and 80%** of patients with gastric cancer present with metastatic disease at diagnosis

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ADVANCED GASTRIC CANCER
First-line Therapy
1ST-LINE TREATMENT ADVANCED GASTRIC CANCER

Recommended Algorithm

Treatment of advanced gastroesophageal cancer
Molecular stratification according to HER2 status

IHC score 0/1

IHC score 2

IHC score 3

ISH-test HER2

ISH−

ISH+

Platin-fluoropyrimidine
+/- docetaxel or epirubicin

Cisplatin-fluoropyrimidine
+ trastuzumab

1ST-LINE TREATMENT ADVANCED GASTRIC CANCER

FACTS

- Chemo-Tx prolongs overall survival
- Chemo-Tx improves symptom control
- Combinations more effective than mono-Tx


- Elderly patients (>70 years) benefit

**1ST-LINE TREATMENT ADVANCED GASTRIC CANCER**

**FACTS**

- Oxaliplatin can substitute for Cisplatin
  Potential advantage for elderly patients
  

- Capecitabin p.o. can substitute for i.v. 5-FU
  Gepoolte analysis: shows higher efficacy
  

- A 3rd drug (triplet) increases the activity and certainly the toxicity
  
  Van Cutsem et al. *J Clin Oncol* 2006; 24: 4991-7
**1ST-LINE CHEMOTHERAPY**

Doublet or Triplet?

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**Docetaxel-CF (DCF) vs CF**

**Response Rate**

37% vs 25%  \( p=0.01 \)

**Time to progression**

5.6 vs 3.7 months \( p<0.001 \)

**Survival**

9.2 vs 8.6 months \( p=0.02 \)

**Grade 3 /4 Toxicity**

69% vs 59% \( p=0.02 \)

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1ST-LINE - JAPAN
Doublet or Triplet?

Unresectable or recurrent gastric cancer

Randomization

Arm A: CS arm
- Cisplatin: 60 mg/m² d8
- S-1: 80, 100, 120 mg*/body d1-21
  repeated every 5 weeks

Arm B: DCS arm
- Docetaxel: 40 mg/m² d1
- Cisplatin: 60 mg/m² d1
- S-1: 80, 100, 120 mg*/body d1-14
  repeated every 4 weeks

*Calculation based on body surface area

Adjustment factors
- Institution
- ECOG PS (0 vs 1)
- Measurable lesion (yes vs no)
- Tumor stage (unresectable vs recurrent)
- Number of metastatic sites (0-1 vs ≥2)
- Histological type (intestinal vs diffuse)

1ST-LINE - JAPAN

Doublet or Triplet?

1ST-LINE - ELDERLY

Doublet or Triplet?

**FLOT 65+ Study** (n=142, median 70 years)

Toxicity Grade 3/4
- FLOT: 81.9%
- FLO: 38.6% (p<0.001)

Deterioration on EORTC Global Health Scale >10 points
- FLOT: 47.5%
- FLO: 20.5% (p<0.01)

Progression-free survival among patients with metastatic disease


Prospective, Randomized, Multicenter, Phase III Study of Fluorouracil, Leucovorin, and Irinotecan Versus Epirubicin, Cisplatin, and Capecitabine in Advanced Gastric Adenocarcinoma: A French Intergroup (Fédération Francophone de Cancérologie Digestive, Fédération Nationale des Centres de Lutte Contre le Cancer, and Groupe Coopérateur Multidisciplinaire en Oncologie) Study

Time to treatment failure better with FOLFIRI but Overall survival equal: 9.5 vs. 9.7 months (p=0.95)
1ST-LINE – ELDERLY PATIENTS
GO2 Study - Full or Reduced Dose Chemotherapy?

Trial design

Phase III, randomised, multi-centre, prospective, controlled, open label, non-inferiority trial

Eligibility
Not fit for full-dose 3-drug chemotherapy, but suitable for reduced intensity chemotherapy.

Follow-up
Total 1 year; 9 weekly imaging and PROMs

Baseline comprehensive geriatric assessment
Including symptoms, fitness, comorbidity, QoL

Decision
(patient / clinician consensus)

Certain that chemotherapy should be used
(BSC not desirable)

"certain randomisation" 1:1:1

OxCap Level A* (100%)
OxCap Level B (80%)
OxCap Level C (60%)

OxCap Level C

Uncertain whether

Uncertain randomisation:
poster session Monday 8-11am
Poster board 156, Swinson et al

Oxaliplatin 130mg/m² day 1 of a 21 day cycle
Capecitabine 625mg/m² bd continuously - given until progression

Hall P et al., ASCO 2019; #4006
1ST-LINE – ELDERLY PATIENTS
GO2 Study - Full or Reduced Dose Chemotherapy?

Results: step 1 - non-inferiority is confirmed

Primary endpoint
Progression Free Survival

Adjusted hazard ratios
Level B vs A 1.09 [95% CI 0.89 - 1.32]
Level C vs A 1.10 [95% CI 0.90 - 1.33]

The non-inferiority boundary of 1.34 is excluded, so non-inferiority is confirmed

Hall P et al., ASCO 2019; #4006
1ST-LINE – ELDERLY PATIENTS
GO2 Study - Full or Reduced Dose Chemotherapy?

Results: step 1 - non-inferiority

Overall survival

Median survival

Level A  7.5 months
Level B  6.7 months
Level C  7.6 months
1ST-LINE – ELDERLY PATIENTS
GO2 Study - Full or Reduced Dose Chemotherapy?

Treatment duration

- Level A
- Level B
- Level C

Mean number of cycles
1ST-LINE – ELDERLY PATIENTS
GO2 Study - Full or Reduced Dose Chemotherapy?

Results step 2: the patient experience

Quality of life

Mean QL improved from baseline to 9 weeks with Level B and Level C

Complete case analysis, adjusted for baseline QoL
RESULTS STEP 2: THE PATIENT EXPERIENCE

Toxicity

% with toxicity

Grade 4  Grade 3  Grade 2  Grade 1  Grade 0

Fatigue  Neuropathy  Nausea  Anorexia  Diarrhoea  Vomiting  PPE  Vein Pain  Stomatitis

Hall P et al., ASCO 2019; #4006

1ST-LINE – ELDERLY PATIENTS

GO2 Study - Full or Reduced Dose Chemotherapy?
1ST-LINE – ELDERLY PATIENTS
GO2 Study - Full or Reduced Dose Chemotherapy?

“Overall Treatment Utility” (OTU) scored after 9 weeks:

- **good OTU**
  - all of:
  - clinician score “benefit”*
  - patient satisfied
  - no major toxicity
  - no drop in QL

- **intermediate OTU**
  - either:
    - clinician score “no benefit”
    - (but patient satisfied and no major toxicity or QL drop)
  - or
    - either patient dissatisfied
    - major toxicity
    - QL deterioration
  - (but clinician scores benefit)

- **poor OTU**
  - both:
    - clinician score “no benefit”
    - patient dissatisfied
    - major toxicity
    - QL deterioration
    - patient has died

NB: decision rules to ensure OTU can be scored in 100% patients

*clinician score of “benefit”: no clinical/radiological evidence of cancer progression and no general health deterioration

drop in QL defined as >16% fall (>2 on the 12-point EORTC global QL scale).

Cocks, K et al., Eur J Cancer (2012) 48, 1713-21


Hall P et al., ASCO 2019; #4006
1ST-LINE – ELDERLY PATIENTS
GO2 Study - Full or Reduced Dose Chemotherapy?

Results step 2: the patient experience

Overall Treatment Utility

Overall treatment utility favours Level C, which had the highest percentage of Good and lowest percentage of Poor OTU scores.

Adjusted odds ratios (trend for better OTU)

Level B vs A 0.87 [95% CI 0.59 - 1.29]

Level C vs A 1.24 [95% CI 0.84 - 1.84]
1ST-LINE – ELDERLY PATIENTS
GO2 Study - Full or Reduced Dose Chemotherapy?

Summary

• This is the largest RCT to date specifically investigating frail/elderly advanced GO cancer patients.

• The lowest dose tested provided
  • non-inferior cancer control (PFS and OS)
  • the best patient experience (OTU, toxicity and QoL)

• No subgroup clearly benefited from higher dose treatment
  • Further work is investigating personalised dose selection based on CGA
Conclusions

- Doublets (Platinum-Fluoropyrimidine) are standard
- No scientific justification for epirubicine-containing triplets
- Docetaxel-containing triplets (DCF, FLOT, …) are indicated in specific situations, e.g. if rapid tumor shrinkage is needed, or if there is an option for secondary resection
- FOLFIRI is a valid alternative to platinum/FP first-line CTx (but not approved in many countries)
- Consider upfront dose-reduction (80% - 60%) in frail and elderly population
ADVANCED GASTRIC CANCER
Second-line Therapy
2ND-LINE TREATMENT ADVANCED GASTRIC CANCER
Recommended Algorithm

**Progression:** evaluation of ECOG performance status, efficacy and tolerability of first-line chemotherapy, patient preferences and the need for remission

- **ECOG PS 0–1**
  - need for remission ++
  - Paclitaxel + ramucirumab

- **ECOG PS 0–2**
  - need for remission +/-
  - Ramucirumab monotherapy or irinotecan monotherapy or taxane monotherapy

- **ECOG PS 2–4 or patient preference**
  - Active symptom control

## 2ND-LINE TREATMENT ADVANCED GASTRIC CANCER
### Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Overall survival, months</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thuss-Patience&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Irinotecan vs. BSC</td>
<td>4.0 vs. 2.4 (p=0.012)</td>
<td>HR 0.48</td>
</tr>
<tr>
<td>AIO Study, Germany (n=40)</td>
<td></td>
<td></td>
<td>∆ 1.6 months</td>
</tr>
<tr>
<td>Kang&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Irinotecan or Docetaxel vs. BSC</td>
<td>5.3 vs. 3.8 (p=0.007)</td>
<td>HR 0.657</td>
</tr>
<tr>
<td>Korean Study (n=202)</td>
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<td></td>
<td>∆ 1.5 months</td>
</tr>
<tr>
<td>Ford&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Docetaxel vs. BSC</td>
<td>5.2 vs. 3.6 (p=0.01)</td>
<td>HR 0.67</td>
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<td>COUGAR-02, UK (n=168)</td>
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<tr>
<td>Hironaka&lt;sup&gt;4&lt;/sup&gt;</td>
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<td>9.5 vs. 8.4 (p=0.38)</td>
<td>HR 1.13</td>
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<td>WJOG, Japan (n=219)</td>
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<td></td>
<td>No difference</td>
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</tbody>
</table>

2ND-LINE TREATMENT ADVANCED GASTRIC CANCER

Survival, Symptom Control, and Quality of Life

Health-related QoL outcomes

Overall survival

Ford HER et al. Lancet Oncol 2014;15:78–86
### 2ND-LINE TREATMENT ADVANCED GASTRIC CANCER

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<td></td>
<td></td>
<td>No difference</td>
</tr>
<tr>
<td>Fuchs⁵</td>
<td>Ramucirumab vs BSC</td>
<td>5.2 vs. 3.8 (p=0.047)</td>
<td>HR 0.776</td>
</tr>
<tr>
<td>REGARD, Global (n=335)</td>
<td></td>
<td></td>
<td>∆ 1.4 months</td>
</tr>
</tbody>
</table>

2ND-LINE TREATMENT ADVANCED GASTRIC CANCER

Anti-Angiogenic Treatment

2ND-LINE TREATMENT ADVANCED GASTRIC CANCER

Rainbow – 2nd-line paclitaxel +/- ramucirumab


<table>
<thead>
<tr>
<th>Comparison</th>
<th>RAM + paclitaxel</th>
<th>Placebo + paclitaxel</th>
<th>HR p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate</td>
<td>28%</td>
<td>16%</td>
<td>p=0.0001</td>
</tr>
<tr>
<td>PFS (med, months)</td>
<td></td>
<td></td>
<td>4.4</td>
</tr>
<tr>
<td>9-month PFS (%)</td>
<td></td>
<td></td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>RAM + paclitaxel</td>
<td>Placebo + paclitaxel</td>
<td>HR 0.635 p&lt;0.0001</td>
</tr>
<tr>
<td>12-month OS (%)</td>
<td></td>
<td></td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td>RAM + paclitaxel</td>
<td>Placebo + paclitaxel</td>
<td>HR 0.807 p=0.0169</td>
</tr>
</tbody>
</table>
## 2ND-LINE TREATMENT ADVANCED GASTRIC CANCER

**RAMIRIS: Ramucirumab + FOLFIRI vs Ramucirumab + Paclitaxel**

### Stratification
- **Inclusion and Exclusion criteria verified**
- **Previous docetaxel-containing therapy**
  - Yes vs. No
- **Time of progression during or after end of first-line therapy**
  - ≤3 months vs. >3 months

### Randomisation
- **Arm A**
  - **Irinotecan 180 mg/m²**
  - **5-FU bolus 400 mg/m²**
  - **Leucovorin 400 mg/m²**
  - **5-FU 2400 mg/m² 46-hour continuous administration day 1 and 15, qd28**
  - **Ramucirumab 8 mg/kg day 1 and 15, qd28**
  - **67 patients**

- **Arm B**
  - **Paclitaxel 80 mg/m² day 1, 8 and 15, qc28**
  - **Ramucirumab 8 mg/kg day 1 and 15, qd28**
  - **34 patients**

### Table: Response Comparison

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Response</th>
<th>FOLFIRI + Ramucirumab</th>
<th>Paclitaxel + Ramucirumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>No previous docetaxel</td>
<td>n</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>CR</td>
<td></td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>PR</td>
<td>1 (7%)</td>
<td>1 (14%)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>8 (57%)</td>
<td>5 (71%)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>5 (36%)</td>
<td>1 (14%)</td>
<td></td>
</tr>
<tr>
<td>Previous docetaxel</td>
<td>n</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>CR</td>
<td></td>
<td>2 (12%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>PR</td>
<td>3 (18%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>6 (35%)</td>
<td>5 (42%)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>6 (35%)</td>
<td>6 (50%)</td>
<td></td>
</tr>
</tbody>
</table>

Lorenzen S et al., ASCO 2019; abstract 4023
2ND-LINE CHEMOTHERAPY FOR ADVANCED GC

Conclusions

- 2nd-line treatment should be offered to patients who are motivated to receive further treatment
- Robust evidence for 2nd-line mono chemotherapy (Evidence IA, ESMO recommendation A)
- Phase-III-data suggest the combination of ramucirumab + paclitaxel to the best available option
- Some evidence for using 2nd-line combinations (like e.g. FOLFIRI)
ADVANCED GASTRIC CANCER
Third-line Therapy
3rd-Line Chemotherapy for Advanced GC

TAS-102 = Trifluridin (FTD) + Tipiracil (TPI)

- Fluorinated Thymidine Incorporation into DNA¹
- DNA Dysfunction¹
- Inhibits Thymidine-Phosphorylase²
- Prolongs FTD degradation²

3RD-LINE CHEMOTHERAPY FOR ADVANCED GC
TAGS Study

Patients with mGC (including GEJ cancer)
- ≥2 prior regimens:
  - Fluoropyrimidine
  - Platinum
  - Taxane and/or irinotecan
  - HER2 inhibitor, if available, for HER2+ disease
  - Refractory to/intolerant of last prior therapy
- ECOG PS of 0 or 1
- Age ≥18 y (≥20 y in Japan)

FTD/TPI + BSC (n=337)
35 mg/m² BID orally on Days 1–5 and 8–12 of each 28-day cycle*

Placebo + BSC (n=170)
BID orally on Days 1–5 and 8–12 of each 28-day cycle*

Stratification: ECOG PS (0/1), region (Japan/ROW), prior ramucirumab (yes/no)

End points
- Primary: OS
- Key secondary: PFS, safety
- Other secondary: ORR, DCR, QOL, time to ECOG PS ≥2

Target 384 events for detection of HR for death of 0.70 with 90% power at 1-sided type 1 error of 0.025

*Treatment until progression, intolerable toxicity, or patient withdrawal

BID, twice daily; DCR, disease control response; FTD/TPI, trifluridine/tipiracil; QOL, quality of life
Shitara K et al. Lancet Oncol. 2018;19:1437–1448
### 3<sup>rd</sup>-LINE CHEMOTHERAPY FOR ADVANCED GC

TAGS Study – Baseline Demographics

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>FTD/TPI (n=337)</th>
<th>Placebo (n=170)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years; median (range)</td>
<td>64.0 (24–89)</td>
<td>62.5 (32–82)</td>
</tr>
<tr>
<td>Gender, %</td>
<td>Male 75</td>
<td>69</td>
</tr>
<tr>
<td>Geographic region, %</td>
<td>Japan 14</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>ROW 86</td>
<td>84</td>
</tr>
<tr>
<td>ECOG PS, %</td>
<td>0 36</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>1 64</td>
<td>60</td>
</tr>
<tr>
<td>Primary site, %</td>
<td>Gastric 71</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>GEJ 29</td>
<td>28</td>
</tr>
<tr>
<td>Prior gastrectomy, %</td>
<td>Yes 44</td>
<td>44</td>
</tr>
<tr>
<td>Number of prior regimens, %</td>
<td>2 37</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>3 40</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>≥4 23</td>
<td>27</td>
</tr>
</tbody>
</table>

ITT population; ECOG PS, Eastern Co-operative Oncology Group Performance Status; FTD/TPI, trifluridine/tipiracil; GEJ, gastroesophageal; ROW, rest of world

Shitara K et al. Lancet Oncol. 2018;19:1437–1448
## 3RD-LINE CHEMOTHERAPY FOR ADVANCED GC
### TAGS Study – Disease Characteristics

<table>
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<tr>
<th>Patient characteristic</th>
<th>FTD/TPI (n=337)</th>
<th>Placebo (n=170)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of metastatic sites, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>46</td>
<td>42</td>
</tr>
<tr>
<td>≥3</td>
<td>54</td>
<td>58</td>
</tr>
<tr>
<td>HER2 status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>Negative</td>
<td>61</td>
<td>62</td>
</tr>
<tr>
<td>Not assessed</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>Prior systemic cancer therapeutic agents, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoropyrimidine</td>
<td>&gt;99&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100</td>
</tr>
<tr>
<td>Platinum</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Irinotecan&lt;sup&gt;b&lt;/sup&gt;</td>
<td>54</td>
<td>58</td>
</tr>
<tr>
<td>Taxane&lt;sup&gt;b&lt;/sup&gt;</td>
<td>92</td>
<td>87</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td>Immunotherapy (anti-PD-1/PD-L1)</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

Shitara K et al. Lancet Oncol. 2018;19:1437–1448
3rd-Line Chemotherapy for Advanced GC

TAGS Study – Survival Outcomes

Overall survival

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<th></th>
<th>FTD/TPI (n=337)</th>
<th>Placebo (n=170)</th>
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<tbody>
<tr>
<td>Events, no. (%)</td>
<td>244 (72)</td>
<td>140 (82)</td>
</tr>
<tr>
<td>Median, months</td>
<td>5.7</td>
<td>3.6</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.69 (0.56-0.85)</td>
<td></td>
</tr>
<tr>
<td>1-sided P</td>
<td>0.0003</td>
<td></td>
</tr>
</tbody>
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Shitara K et al. Lancet Oncol. 2018;19:1437–1448
### 3rd-Line Chemotherapy for Advanced GC

**TAGS Study – Adverse Events in >10% of patients**

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<tbody>
<tr>
<td></td>
<td>Any grade, %</td>
<td>Grade ≥3, %</td>
</tr>
<tr>
<td>Nausea</td>
<td>37</td>
<td>3</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>34</td>
<td>9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27</td>
<td>7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td>Asthenia</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>General physical deterioration</td>
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</tr>
</tbody>
</table>

All treated patients
FTD/TPI, trifluridine/tipiracil

Shitara K et al. Lancet Oncol. 2018;19:1437–1448
Grade ≥3 febrile neutropenia was reported in 6 patients (2%) treated with FTD/TPI

*Treated patients with ≥1 post-baseline measurement
FTD/TPI, trifluridine/tipiracil

Shitara K et al. Lancet Oncol. 2018;19:1437–1448
CONCLUSIONS FOR TREATMENT OF ADVANCED GC
My Best Choice

- **First-line Platinum-Fluoropyrimidin-Doublet** (triplet = exception)
  - Irinotecan-5-FU: is an alternative (not approved) in Platin-pretreated pts
- Plan for sequential treatment lines
- **Second-line Paclitaxel-Ramucirumab** (standard)
- **Third-line TAS-102** (now FDA approved, positive EMA CHMP opinion)
- **Personalized therapy**
  - HER2-positive: Chemo + Trastuzumab (only first-line)
  - Anti-Claudin18.2 (Zolbetuximab) in clinical trials
  - Immunotherapy in selected pts in clinical trials