TAGS: A Phase 3, Randomised, Double-blind Study of Trifluridine/Tipiracil (TAS-102) Versus Placebo in Patients With Refractory Metastatic Gastric Cancer

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Disclosures

• No conflict of interests to report
Introduction

• GC is the fifth most common cancer worldwide and the third most common cause of cancer-related death\(^1\)

• Most patients with GC present with advanced or metastatic disease,\(^2\) which has a poor prognosis (5-year OS rate, 4%)\(^3\)

• There is a high unmet medical need in pretreated patients with advanced or metastatic GC
  – Approved third-line treatment options are limited

• Trifluridine/tipiracil (FTD/TPI) is a novel oral therapy comprising the thymidine analog trifluridine, and tipiracil, which prevents trifluridine degradation

• FTD/TPI is approved for mCRC, based on results of the phase 3 RECOURSE trial\(^4\)
  – Median OS was 7.1 months with FTD/TPI vs 5.3 months with placebo (HR: 0.68)

• A phase 2 Japanese study (EPOC1201) evaluated FTD/TPI in mGC after failure of standard chemotherapies, including fluoropyrimidines, platinum, and taxanes or irinotecan\(^5\)
  – Median OS was 8.7 months; DCR was 65.5%
TAGS: TAS-102 Gastric Study\textsuperscript{a}

**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)

**Target sample size:** 500

**Endpoints**
- **Primary:**
  - OS
- **Key secondary:**
  - PFS, safety
- **Other secondary:**
  - ORR
  - DCR
  - QOL
  - Time to ECOG PS ≥2

**FTD/TPI (TAS-102) + BSC (n=337)**
- 35 mg/m\(^2\) 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

**Patients with mGC**
- Treatment until progression, intolerable toxicity, or patient withdrawal
- Multicentre, randomised, double-blind, placebo-controlled, phase 3 study
  - Stratification: ECOG PS (0 vs 1), region (Japan vs ROW), prior ramucirumab (yes vs no)
  - Sites: 17 countries, 110 sites; enrolment: February 2016 – January 2018
  - Data cutoff date: March 31, 2018
  - 384 events were targeted to allowed detection of a HR for death of 0.70 with 90% power at 1-sided type 1 error of 0.025

\textsuperscript{a}NCT02500043

BID, twice daily; BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ORR, objective response rate; PFS, progression-free survival; QOL, quality of life; R, randomised; ROW, rest of world
## Baseline Demographic and Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>FTD/TPI (n=337)(^a)</th>
<th>Placebo (n=170)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years; median (range)</td>
<td>64 (24–89)</td>
<td>62 (32–82)</td>
</tr>
<tr>
<td>Gender, %</td>
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<td>Male 69</td>
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<td>Geographic region, %</td>
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<td>USA 3</td>
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<tr>
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<td>Europe 80</td>
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<td></td>
<td>Japan 14</td>
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<td>ECOG PS, %</td>
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<td>0 40</td>
</tr>
<tr>
<td></td>
<td>1 64</td>
<td>1 60</td>
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<td>Primary site, %</td>
<td>Gastric 71</td>
<td>Gastric 71</td>
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<tr>
<td></td>
<td>GEJ 29</td>
<td>GEJ 28</td>
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<tr>
<td></td>
<td>Both 0</td>
<td>Both 1</td>
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<tr>
<td>Prior gastrectomy, %</td>
<td>Yes 44</td>
<td>Yes 44</td>
</tr>
<tr>
<td>Number of prior regimens, %</td>
<td>2 37</td>
<td>3 38</td>
</tr>
<tr>
<td></td>
<td>3 40</td>
<td>3 35</td>
</tr>
<tr>
<td></td>
<td>≥4 23</td>
<td>≥4 27</td>
</tr>
</tbody>
</table>

\(^a\)ITT population

**ITT**, intent to treat
# Baseline Disease Characteristics and Post-Study Therapy

<table>
<thead>
<tr>
<th></th>
<th>FTD/TPI (n=337)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Placebo (n=170)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of metastatic sites, %</strong></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>
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<tr>
<td><strong>HER2 status, %</strong></td>
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</tr>
<tr>
<td>Positive</td>
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<tr>
<td>Negative</td>
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<td>62</td>
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<tr>
<td>Not assessed/unknown</td>
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<td><strong>Prior systemic cancer therapeutic agents, %</strong></td>
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<td>Fluoropyrimidine</td>
<td>&gt;99&lt;sup&gt;b&lt;/sup&gt;</td>
<td>100</td>
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<td>Taxane&lt;sup&gt;c&lt;/sup&gt;</td>
<td>92</td>
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<td>Irinotecan&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>Immunotherapy (anti–PD-1/PD-L1)</td>
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<tr>
<td><strong>Post-study systemic anticancer therapy, %</strong></td>
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</tbody>
</table>

<sup>a</sup>ITT population; <sup>b</sup>1 patient did not receive a fluoropyrimidine; <sup>c</sup>All patients received irinotecan or taxane or both
Primary Endpoint – OS

Events, no. (%)

- **FTD/TPI (n=337)a**
  - 244 (72)
- **Placebo (n=170)a**
  - 140 (82)

Median, months

- **FTD/TPI**
  - 5.7
- **Placebo**
  - 3.6

HR (95% CI)

- **FTD/TPI**
  - 0.69 (0.56–0.85)

One-sided \( P \)

- 0.0003

Two-sided \( P \)

- 0.0006

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<table>
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\( ^a \)ITT population; \(^b\)Stratified log-rank test
OS Subgroup Analysis

- Multivariate analysis showed several factors to be prognostic ($P<0.05$): ECOG PS (0 vs 1), age (<65 vs ≥65 y), prior regimens (2 vs ≥3), metastatic sites (1 or 2 vs ≥3), and HER2 status (negative vs positive or not done)
- After adjusting for these factors, the treatment effect for FTD/TPI was maintained (HR: 0.69; 95% CI: 0.56–0.85)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup</th>
<th>Patients</th>
<th>HR (95% CI)</th>
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<td>HER2 status</td>
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<th>Variable</th>
<th>Subgroup</th>
<th>Patients</th>
<th>HR (95% CI)</th>
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</table>

*Two patients had primary lesions at both sites; this subgroup was not analysed for OS due to insufficient size; †HER2 status was not available/unknown for 100 patients; results for these patients are not shown.
Secondary Endpoint – PFS

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>FTD/TPI</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>337</td>
<td>170</td>
</tr>
<tr>
<td>1</td>
<td>314</td>
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<tr>
<td>14</td>
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</table>

**Events, no. (%)**
- FTD/TPI: 287 (85)
- Placebo: 156 (92)

**Median, months**
- FTD/TPI: 2.0
- Placebo: 1.8

**HR (95% CI)**
- FTD/TPI: 0.57 (0.47–0.70)
- Placebo: <0.0001

**Two-sided P**
- FTD/TPI: <0.0001

*ITT population; *Stratified log-rank test
## PFS Subgroup Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
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</table>

[Two patients had primary lesions at both sites; this subgroup was not analysed for PFS due to insufficient size; HER2 status was not available/unknown for 100 patients; results for these patients are not shown]
## Secondary Endpoints – ORR and DCR

<table>
<thead>
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<th>FTD/TPI (n=290)</th>
<th>Placebo (n=145)</th>
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<tbody>
<tr>
<td><strong>ORR, n (%)</strong></td>
<td>13 (4)</td>
<td>3 (2)</td>
</tr>
<tr>
<td><strong>DCR, n (%)</strong></td>
<td>128 (44)</td>
<td>21 (14)</td>
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<tr>
<td>Complete response</td>
<td>1 (&lt;1)</td>
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<tr>
<td>Partial response</td>
<td>12 (4)</td>
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<tr>
<td><strong>Stable disease</strong></td>
<td>115 (40)</td>
<td>18 (12)</td>
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<tr>
<td><strong>Difference in DCR, % (95% CI)</strong></td>
<td>30 (22–38)</td>
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<td>Two-sided P value</td>
<td>&lt;0.0001</td>
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Secondary Endpoint – Time to Deterioration of ECOG Performance Status to ≥2

Events, no. (%)  
FTD/TPI *(n=337)*  
Placebo *(n=170)*

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<th>FTD/TPI</th>
<th>Placebo</th>
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<td>264 (78)</td>
<td>145 (85)</td>
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Median, months  

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HR (95% CI)  

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<th>FTD/TPI</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.69 (0.56–0.85)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Two-sided *P*  

<table>
<thead>
<tr>
<th>Two-sided <em>P</em></th>
<th>FTD/TPI</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0005</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ITT population; *Stratified log-rank test*
Safety Overview

<table>
<thead>
<tr>
<th>Safety Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any AE of any cause</strong></td>
</tr>
<tr>
<td>%</td>
</tr>
<tr>
<td>Any AE of any cause</td>
</tr>
<tr>
<td>Any serious AE of any cause</td>
</tr>
<tr>
<td>Any treatment-related AE</td>
</tr>
<tr>
<td>Most common AEs of any cause</td>
</tr>
<tr>
<td>Anaemia and/or decreased haemoglobin level</td>
</tr>
<tr>
<td>Neutropenia and/or decreased neutrophil count</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Leucopenia and/or decreased white blood cell count</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Asthenia</td>
</tr>
<tr>
<td>Thrombocytopenia and/or decreased platelet count</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Dyspnoea</td>
</tr>
<tr>
<td>General physical health deterioration</td>
</tr>
</tbody>
</table>

• Grade ≥3 febrile neutropenia of any cause was reported in 6 patients (2%) treated with FTD/TPI

---

a All treated patients; b Grade 5 AEs considered related to treatment were reported in one (<1%) patient in the FTD/TPI group (attributed to cardiopulmonary arrest) and one (1%) patient in the placebo group (attributed to toxic hepatitis); c AEs of any grade that occurred in ≥10% of patients in either treatment group
Management of AEs (Any Cause)

<table>
<thead>
<tr>
<th>Action taken due to AEs (any grade)</th>
<th>FTD/TPI (n=335)(^a) %</th>
<th>Placebo (n=168)(^a) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing modification (dosing delay or dose reduction)</td>
<td>58</td>
<td>22</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Treatment discontinuation</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>G-CSF treatment for neutropenia</td>
<td>16</td>
<td>2</td>
</tr>
</tbody>
</table>

**Most common AEs leading to dosing modification**\(^b\)

<table>
<thead>
<tr>
<th>Most common AEs leading to dosing modification</th>
<th>FTD/TPI (n=335)(^a) %</th>
<th>Placebo (n=168)(^a) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia and/or decreased neutrophil count</td>
<td>37</td>
<td>25</td>
</tr>
<tr>
<td>Anaemia and/or decreased haemoglobin level</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Leucopenia and/or decreased white blood cell count</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

- Dosing delay without dose reduction was used more frequently than dose reduction to manage AEs

\(^a\)All treated patients; \(^b\)AEs of any grade that occurred in 5% or more of patients in either treatment group
Conclusions

- FTD/TPI showed a clinically meaningful and statistically significant improvement in OS and PFS compared with placebo in heavily pretreated patients with advanced gastric or GEJ cancer
  - 31% reduction in risk of death (HR: 0.69; 95% CI: 0.56–0.85; one-sided \( P=0.0003 \); two-sided \( P=0.0006 \))
  - 2.1-month improvement in median OS (5.7 vs 3.6 months)
- Patients in the FTD/TPI group had a higher DCR (44% vs 14%; two-sided \( P<0.0001 \)) and lower risk of ECOG PS deterioration to ≥2 (HR: 0.69; 95% CI: 0.56–0.85; two-sided \( P=0.0005 \))
- FTD/TPI showed a predictable and manageable safety profile, consistent with that seen previously in patients with mCRC
  - Dosing delays were used more frequently than dose reduction to manage AEs
  - No new safety signals were observed in patients with mGC
- FTD/TPI represents an effective new treatment option with a manageable safety profile for heavily pretreated patients with advanced gastric or GEJ cancer
Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial

Kohei Shitara, Toshihiko Doi, Mikhail Dvorkin, Wasat Mansoor, Hendrik-Tobias Arkenau, Aliaksandr Prokharau, Maria Alsina, Michele Ghidini, Catia Faustino, Vera Gorbunova, Edvard Zhavrid, Kazuhiro Nishikawa, Ayumu Hosokawa, Şuayib Yalçın, Kazumasa Fujitani, Giordano D Beretta, Eric Van Cutsem, Robert E Winkler, Lukas Makris, David H Ilson, Josep Tabernero
We thank the patients and families who made this trial possible and the clinical study teams who were involved in this trial, as well as the data and safety monitoring board members.

This study was funded by Taiho Oncology, Inc. and Taiho Pharmaceutical Co., Ltd.

Professional medical writing and editorial assistance were provided by Mark Palangio at Scientific Connexions (Lyndhurst, NJ, USA) and funded by Taiho Oncology, Inc.
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