Trifluridine/tipiracil in metastatic colorectal cancer: an updated multicentre real-world analysis on efficacy, safety and predictive factors

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1. Guy's and St Thomas' NHS foundation Trust, London; 2. Maidstone and Tunbridge Wells NHS Trust, Maidstone; 3. Southamptom University Hospitals NHS Trust, Southamptom; 4. Leicester Royal Infirmary, Leicester; 5. Poole Hospital NHS Foundation Trust, Poole; 6. Queen's Hospital, Essex; 7. Beaslon West of Scotland Cancer Centre, Glasgow; 8. University College London Cancer Institute, London; 9. Leicester Cancer Centre, University of Leicester

Abstract 3136

ABSTRACT

Background: The orally administered combination Trifluridine and Tipiracil hydrochloride (TAS-102) has been approved as third line therapy in metastatic colorectal cancer, demonstrating survival benefit and acceptable toxicity profile in the phase III RECURSEE study.1,2 Methods: We performed an updated multicenter retrospective observational study of patients with metastatic colorectal cancer receiving TAS-102 as third line therapy between 2016 and 2019 in 8 cancer centers across the UK. Medical records were reviewed for clinicopathological characteristics, treatment, survival and toxicity outcomes. Prognostic and predictive factors were identified using uni- and multivariate regression analyses. Results: A total of 236 patients were included. Median age was 69 years (31-89). All patients had received at least 2 lines of fluoropyrimidine-based chemotherapy doublet with oxaliplatin or irinotecan. About 10% of patients had ECOG > 2. Median duration of TAS-102 treatment was 3 months (0.2-25.9), with an ORR of 21.1% and disease control rate of 79.1%. Median OS was 7.6 months (95% CI 6.5-8.8) and median PFS 3.3 months (95% CI 3.0-3.5). A dose reduction was required in 27% of patients, while 76% discontinue treatment due to toxicity. Neutropenia was present in 59% (≥3 34%) with 4.6% cases of neutropenic fever. Thrombocytopenia was less frequent 11% (≥3 1.6%) Fatigue was reported in 67% (≥3 9%), nausea 30% (≥3 3.3%) and diarrhoea 24.5% (≥3 2.3%), Baseline Neutrophil to Lymphocyte ratio (NLR) <5 and CEA <200 had favourable prognostic values (HR: 0.52 and 0.39, p<0.001) and predictive value (OR: 5.94 and 5.08, p=0.05). Development of ≥3 neutropenia during treatment predicted treatment response (OR: 3.08, p<0.001) and better OS (HR: 0.44, p<0.001). Following TAS-102 treatment 41% were referred for Phase I trial or re-challenged with chemotherapy. Conclusions: These results are consistent with the efficacy and toxicity outcomes from RECURSEE study. However, lower disease control rates and higher rates of dose reductions are seen in the real-world population. Pre-treatment NLR and CEA could serve as potential markers for patient selection. Prospective OBJECTIVES

To assess efficacy and adverse event profile of TAS-102 in clinical practice in comparison to RECURSEE trial and identify predictors of response.

METHODS

• Retrospective observational study using patient medical records.
• Data were collected on patient demographics, ECOG performance status, site of disease, presence of KRAS mutation, previous treatment, toxicities and treatment outcomes associated with Trifluridine/Tipiracil.
• Patients with metastatic colorectal cancer receiving TAS-102 as 3rd line therapy between January 2016 and January 2019 in eight cancer centers across the UK.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=236</th>
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<tr>
<td>Age - years (%)</td>
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<tr>
<td>Median</td>
<td>65</td>
</tr>
<tr>
<td>&lt; 65</td>
<td>86</td>
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<tr>
<td>65 and above</td>
<td>156</td>
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Table 2. Predictors of response to TAS-102

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Model</th>
<th>Multivariate Model</th>
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</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>P</td>
<td>ORR (95% CI)</td>
</tr>
<tr>
<td>Age &lt;65</td>
<td>0.67 (0.2-2.9)</td>
<td>0.40</td>
</tr>
<tr>
<td>Alb &lt;35</td>
<td>0.18 (0.1-1.2)</td>
<td>0.12</td>
</tr>
<tr>
<td>PS ≤1</td>
<td>0.02 (4.7-12.7)</td>
<td>0.26</td>
</tr>
<tr>
<td>NLR ≤5</td>
<td>1.06 (0.8-1.2)</td>
<td>0.005</td>
</tr>
<tr>
<td>PLR ≤300</td>
<td>0.94 (0.8-1.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>CEA ≤200</td>
<td>0.30 (0.2-0.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>Neutropenia (≥3)</td>
<td>1.6 (1.4-1.8)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

CONCLUSIONS

• OS, PFS and ORR observed in our real-world experience were consistent with the RECURSEE trial though we noted a lower disease control rate.
• Overall, TAS-102 was well tolerated and the most prevalent adverse events seen in our patients were in keeping with those reported in the trial (haematological and GI toxicities).
• Pre treatment Neutrophil to Lymphocyte ratio (NLR)<5 and CEA<200 had a favourable prognostic and predictive value.
• Development of ≥3 neutropenia during treatment predicted treatment response and better survival outcomes.

REFERENCES


Email: chara.stavroula@kcl.ac.uk
Early response evaluation and CEA response in patients treated in a Danish randomized study comparing trifluridine/tipiracil (TAS-102) with or without bevacizumab in patients with chemorefractory metastatic colorectal cancer (mCRC).

**Key Findings**
- The combination of trifluridine/tipiracil with bevacizumab prolongs PFS and OS in patients with refractory metastatic colorectal cancer.
- Early evaluation (before second cycle) can prevent unnecessary treatment in 14% of patients.
- Early change in CEA is a prognostic marker.

**Introduction**

**Material & Methods**

- **Main inclusion criteria:**
  - Histologically confirmed mCRC, PS 0-1, informed consent
  - PD during or after therapy with fluoropyrimidine, irinotecan, oxaliplatin and EGFR-inhibitor (RAS wildtype, prior bevacizumab was optional)

- The primary endpoint was PFS. The aim was to increase PFS from 1.8 to 3.8 months. Secondary objectives included OS and toxicity. Cut-off date was Feb 15, 2019, and all analyses were based on intention-to-treat.

- Changes in CEA were defined as:
  - **CEA decrease:** CEA decreased at least 25% from baseline to 1 months evaluation
  - **CEA stable:** CEA decreased or increased less than 25%
  - **CEA increase:** CEA increased at least 25% from baseline to 1 months evaluation

**Study design**

- **FTD / TPI**
  - 35 mg/m² orally twice daily, days 1-5 + 8-12 q 4 w

- **FTD / TPI + bevacizumab**
  - 35 mg/m² orally twice daily, days 1-5 + 8-12 q 4 w
  - Bevacizumab: 5 mg/kg q 2 w

**Study diagram**

**Results**

- 93 patients were randomized from Aug 2017 to Oct 2018
- Median PFS was significantly prolonged from 2.6 months (FTD/TPI) to 4.6 months (FTD/TPI + bevacizumab) with a hazard ratio (HR) 0.45 (95% CI, 0.29-0.72; p = 0.001)
- Median OS was significantly prolonged from 6.7 months (FTD/TPI) to 9.4 months (FTD/TPI + bevacizumab) with a hazard ratio (HR) 0.55 (95% CI, 0.32-0.94; p = 0.03)
- Therapy was well tolerated, patients receiving FTD/TPI + bevacizumab had more grade 3-4 neutropenia (67% vs 38%, p=0.01) but only 3 patients developed febrile neutropenia.
- 28 patients had early PD (within 2 mo); hereof 7 clinical PD and 21 with RECIST PD
- 13 patients had early PD (within 1 mo); hereof 2 clinical PD and 11 with RECIST PD

**Table 1. Baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>FTD/TPI</th>
<th>FTD/TPI+bev</th>
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<tbody>
<tr>
<td>Number of patients</td>
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<td>46</td>
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<tr>
<td>Age, years (median, range)</td>
<td>67 (45-82)</td>
<td>64 (40-83)</td>
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<td>Sex (male/female)</td>
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<td>24/22</td>
</tr>
<tr>
<td>Performance status (0/1)</td>
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<td>23/23</td>
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<tr>
<td>Sidedness (left/right)</td>
<td>36/13</td>
<td>35/11</td>
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<tr>
<td>RASmut (yes/no)</td>
<td>29/18</td>
<td>27/19</td>
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<tr>
<td>Prior lines of palliative therapy ≤ 2</td>
<td>20 (42%)</td>
<td>21 (46%)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>9 (18%)</td>
<td>12 (25%)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>14 (30%)</td>
<td>13 (28%)</td>
</tr>
<tr>
<td>Prior bevacizumab</td>
<td>20 (43%)</td>
<td>27 (58%)</td>
</tr>
<tr>
<td>Last line before FTD/TPI</td>
<td>36 (77%)</td>
<td>39 (85%)</td>
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**Table 2. CEA response**

<table>
<thead>
<tr>
<th></th>
<th>CEA decrease</th>
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<tr>
<td>Number</td>
<td>9</td>
<td>25</td>
<td>31</td>
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<tr>
<td>Median PFS, months</td>
<td>7.8</td>
<td>3.7</td>
<td>2.8</td>
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<tr>
<td>Median OS, months</td>
<td>NR</td>
<td>9.4</td>
<td>6.7</td>
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**Table 3. Early PD**

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<th>Early PD (within 2 mo)</th>
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<td>Patients, n (%)</td>
<td>28 (30%)</td>
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<tr>
<td>PS 0, n (%)</td>
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</tr>
<tr>
<td>PS 1, n (%)</td>
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<td>CEA baseline (median µg/L)</td>
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<td>LDH baseline (median U/L)</td>
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<td>256</td>
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<td>Months with metastatic disease</td>
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<td>Prior bevacizumab</td>
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<td>52 (80%)</td>
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<tr>
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<td>13 (20%)</td>
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<tr>
<td>Evaluable CEA, n (%)</td>
<td>18 (64%)</td>
<td>47 (72%)</td>
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<td>CEA increase 1 month from baseline, median % (range)</td>
<td>43% (6-307%)</td>
<td>19% (-60-150%)</td>
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<tr>
<td>PFS (median, months)</td>
<td>1.1</td>
<td>4.6</td>
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<tr>
<td>OS (median, months)</td>
<td>5.5</td>
<td>9.8</td>
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This investigator-initiated study was supported in part by Servier.
Background
The clinical benefit of trifluridine/tipiracil (FTD/TPI) was elucidated in RCTs, REDUCED1 and TERRA1, and FTD/TPI became one of the standard treatment for metastatic colorectal cancer (mCRC) in the late-line setting.

Several combination therapies with FTD/TPI have been investigated. Among them, the combination therapy of FTD/TPI with bevacizumab (BEV) showed the promising efficacy for previously treated mCRC in the phase IIb study3.

Although the sample size of this study was small, some differences of the efficacy were existing depending on RAS mutation status.

C-STAR FORCE Study
Phase IIb study of FTD/TPI + BEV for previously treated mCRC.

Objective
To investigate the efficacy and safety of the combination therapy of FTD/TPI with BEV for previously treated mCRC as RAS mutation status.

Conclusion
FTD/TPI combined with BEV showed promising efficacy with an acceptable safety profile for previously treated mCRC regardless RAS mutation status, although OCR was higher in RAS wild-type.

Acknowledgements
This study was supported by the Japanese Foundation for Multimodal Treatment of Colon (JFMC) with funding from Taiho Pharmaceutical Co. Ltd. Japan under the research contract.

References
Bevacizumab plus trifluridine/tipiracil in elderly patients with previously untreated metastatic colorectal cancer (KSCC 1602): A single-arm, Phase 2 study

1. Akita Makiyama, 1Eiji Oki, 1Yuji Miyamoto, 1Masahito Kotaka, 1Hirofumi Kawanaka, 1Keisuke Miwa, 1Akira Kabashima, 1Tomohiro Noguchi, 1Kotaro Yuge, 1Tomomi Kashiwada, 1Mototsugu Shimokawa, 1Hiroshi Saeo, 1Yoshito Akagi, 1Hideo Baba, 1Masaki Mori, 1Kyushu Study Group of Clinical Cancer (KSCC), 1Department of Hematology/Oncoology, 1Japan Community Health Care Organization Kyushu Hospital, 1Department of Surgery and Science, 1Graduate School of Medical Sciences, 1Kumamoto University, 1Department of Gastroenterological Surgery, 1Graduate School of Medical Sciences, 1Kumamoto University, 1Sano, 1Clinical Research Institute and Department of Surgery, 1National Hospital Organization Beppu Medical Center, 1Multidisciplinary Treatment Cancer Center, 1Kumamoto University Hospital, 1Department of Surgery, 1National Oita Medical Center, 1Department of Surgery, 1Sakuragaoka general Hospital, 1Department of Surgery, 1Sakuragaoka Hospital, 1Kumamoto University Hospital, 1Department of General Surgery, 1Kumamoto University, 1Department of Surgery, 1Kumamoto University School of Medicine.

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Background

- Elderly patients often cannot tolerate the usual combination of two cytotoxic agents.
- Recently, bevacizumab plus trifluridine/tipiracil (FTD/TP) was shown to be a good candidate regimen for vulnerable patients.

Objective

- We aimed to assess the efficacy and safety of bevacizumab plus FTD/TP in elderly patients with metastatic colorectal cancer.

Patients and Methods:

Study Treatment

Bevacizumab (5 mg/kg)

Endpoints and Statistical design

Primary endpoint: progression-free survival (PPS) Secondary endpoints: overall survival, response rate, safety profile

Statistical design: Assuming a null hypothesis of 5 month PFS and an alternative hypothesis of 9 month PFS with one sided type I error of 0.1 and type II error of 0.2, it was necessary to enroll a minimum 32 patients in the final evaluation.

Key Eligibility Criteria

1. ≥70 years on the day registration
2. Histologically confirmed metastatic colorectal adenocarcinoma
3. No history of previous chemotherapy, immunotherapy, or radiation therapy excluding adjuvant chemotherapy
4. Measurable disease (RECIST v.1.1)
5. ECOG performance status of 0 or 1
6. Other of following:
   - Fit: Physician and patient decided not to use the standard therapy although it is applicable
   - Vulnerable: The patient could not receive standard therapy similar to the young people but could receive some kind of treatment
7. Adequate organ function

Flow Chart

- All enrolled patients N=99
- Treated patients N=99
- Safety analysis N=99
- Progression-free Survival
- Overall Survival
- Results
- mPFS: 8.0 months
- mOS: Not reached

Baseline Characteristics

<table>
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<tr>
<th>Variable</th>
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<td>76.0</td>
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<td>(Min-Max)</td>
<td>(70-88)</td>
<td>(70-88)</td>
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<td>Sex</td>
<td>Male</td>
<td>17 (43.6)</td>
<td>15 (40.5)</td>
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<td>4 (8.5)</td>
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</tr>
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<td>4</td>
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<td>1 (2.2)</td>
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<td>6 (16.2)</td>
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<td>Rectum</td>
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<td>13 (35.1)</td>
<td></td>
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<td></td>
<td>Tub</td>
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<td>30 (81.0)</td>
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<td>Por</td>
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<td>3 (12.3)</td>
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<td></td>
<td>Mac</td>
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<td>2 (5.1)</td>
<td></td>
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<td></td>
<td>Wild</td>
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<td>9 (27.9)</td>
<td></td>
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<td>21 (60.8)</td>
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<td>6 (16.2)</td>
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<td>Geriatric fit</td>
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<td>18 (46.0)</td>
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</tr>
</tbody>
</table>

Subgroup Analysis (PPS)

- CR: 0 (0)
- PR: 15 (40.5)
- SD: 17 (43.5)
- PD: 3 (8.1)
- NE: 2 (5.4)
- ORR: 15 (95%CI: 41.1-75.1)
- DCR: 32 (86.5)

Conclusion

- In this Phase 2 KSCC 1602 trial of bevacizumab plus FTD/TP, the primary endpoint of PFS was achieved.
- This combination therapy showed favorable survival outcomes with an acceptable safety profile for elderly patients with previously untreated metastatic colorectal cancer.

Acknowledgement

- Name of the primary sponsor: Kyushu Study Group of Clinical Cancer (KSCC)
- We thank all the patients, their families, and collaborators from 17 institutions.
- This study was financially supported by Taiho Pharmaceutical Co., Ltd.

Participating institutions:
- Kyushu University Hospital
- OCHI Kyushu Hospital
- Kurume University Hospital
- Kumamoto University
- National Oita Medical Center
- Kagoshima Municipal Hospital
- Saga University Hospital
- National Beppu Medical Center
- Imabari Hospital
- Kochi Hospital
- Kagoshima Chuo Hospital
- Kuma Hospital
- Hiroshima Red Cross Hospital
- Miki Hospital
- Hikone Hospital
- Kokura Hospital
- Oita City Medical Center
- General Hospital
- Sano Hospital
**Abstract**

A PHASE III, RANDOMISED, OPEN-LABEL STUDY OF TRIFLURIDINE/TIPIRACIL＋BEVACIZUMAB VERSUS CAPECITABINE＋BEVACIZUMAB FOR THE FIRST-LINE TREATMENT OF PATIENTS WITH UNRESECTABLE METASTATIC COLORECTAL CANCER WHO ARE NOT CANDIDATES FOR INTENSIVE THERAPY


**Background**

- There is a clear unmet need for effective first-line treatment for patients with metastatic colorectal cancer (mCRC) who are not candidates for intensive therapy owing to their age, performance status, low tumour burden, comorbidities or non-clinical reasons.

- We initiated the phase III SOLSTICE study following promising anti-tumour activity demonstrated with the combination of trifluridine/tipiracil plus bevacizumab in this patient population in the phase II TASC01 study.

- SOLSTICE will compare the efficacy of trifluridine/tipiracil plus bevacizumab with that of capecitabine plus bevacizumab in the first-line setting in patients with unresectable mCRC who are not candidates for intensive therapy. The planned enrolment includes 854 patients from approximately 200 centres in 25 countries.

**Rationale**

- Bevacizumab, a VEGF endothelial growth factor-targeted agent, inhibits angiogenesis and may normalize tumour vessel function and blood flow. It has been reported that combining bevacizumab with chemotherapy improves outcome in combination with trifluridine/tipiracil. The clinical development of trifluridine/tipiracil in metastatic colorectal cancer (mCRC) has been driven by the high prevalence of mCRC in Japan. Trifluridine/tipiracil has also extensively been approved in Europe and in Japan for mCRC.

- The mechanism of action of trifluridine/tipiracil differs from that of 5-fluorouracil. By initiating thymidylate phosphorylation, trifluridine prevents the de novo formation of thymidylate, thereby improving incorporation of thymidylate into DNA and tumour cell death in DNA synthesis. 

- Trifluridine/tipiracil is approved in several countries and regions, including Japan, the USA, and the European Union, for use in previously treated mCRC patients. Trifluridine/tipiracil has also been approved in the USA for use in previously treated patients with metastatic gallbladder cancer (GBC) in gastrointestinal junction adenocarcinomas. Trifluridine/tipiracil has also recently been approved in Europe and in Japan for mCRC.

**Methods**

- **Design and patients**
  - SOLSTICE is a phase III, international, open-label, randomized trial comparing a fixed-dose combination of trifluridine/tipiracil (3 g/m² per day) and bevacizumab (15 mg/kg every 2 weeks) versus capecitabine (1000 mg/m² per day on days 1-14 and 1 cycle) and bevacizumab (15 mg/kg every 2 weeks) in patients with unresectable mCRC who are not candidates for intensive therapy, according to the investigator's judgement (Figure 1, Table 1).
  - The planned enrollment includes 854 patients. Based on TASC01 results, it was hypothesized that a sample size of approximately 850 patients is required to demonstrate statistical significance in the primary endpoint of progression-free survival.
  - Patients will be randomly allocated to treatment in a 1:1 ratio (Figure 1), stratified by Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 vs 1, baseline lactate dehydrogenase (LDH) ≤ upper limit of normal (ULN), and reason for non-eligibility for intensive therapy due to clinical condition or non-clinical condition.

- **Endpoints and assessments**
  - The primary endpoint of SOLSTICE is to demonstrate the superiority of T/T-B over C/B in terms of progression-free survival, based on investigator assessment (confirmed by imaging central reading) (Figure 1).
  - The key secondary endpoint is overall survival. Other secondary endpoints include overall response rate, disease control rate, duration of response, quality of life, safety and tolerability. Additionally, an exploratory objective is to analyze efficacy according to ECOG PS, BRAF and microsatellite instability status.

- **Disclosures**
  - Curative assessment (radiological images assessed locally) and currently according to RECIST 1.1 criteria will be performed every 6 weeks until progression, death or initiation of a new palliative treatment (whichever occurs first).

- **Safety** will be assessed throughout the study period and graded and recorded according to the National Cancer Institute Common Toxicity Criteria (version 4.0).

- **Acknowledgements**
  - The authors acknowledge the contributions of the study participants, the investigators, and the study teams.

- **References**
  - A randomized, open-label, phase III trial of bevacizumab plus the fixed-dose combination of trifluridine/tipiracil (3 g/m² per day) versus capecitabine (1000 mg/m² per day on days 1-14, 1 cycle) and bevacizumab (15 mg/kg every 2 weeks) in patients with unresectable mCRC who are not candidates for intensive therapy, according to the investigator's judgement.

- **Key take-aways**
  - The mechanism of action of trifluridine/tipiracil differs from that of 5-fluorouracil. By initiating thymidylate phosphorylation, trifluridine prevents the de novo formation of thymidylate, thereby improving incorporation of thymidylate into DNA and tumour cell death in DNA synthesis.

- **Figure 1. SOLSTICE study design.**
  - Randomization
  - Patients with mCRC not candidates for intensive therapy in 114-line
  - N.B.: Any patient with mCRC who is not candidates for intensive therapy in 114-line
  - Maintenance therapy
  - Endpoints
  - Primary
  - Progression-free survival
  - Key secondary
  - Overall survival
  - Other Secondary
  - Disease control rate
  - Duration of response
  - Safety and tolerability
  - Efficacy according to ECOG PS, BRAF, MSI status

- **Table 1. Key patient eligibility criteria.**
  - Key eligibility criteria
  - Advanced or metastatic colorectal cancer patients for whom the use of chemotherapy is not feasible or have not responded to previous chemotherapy
  - Age ≥ 18 years
  - Eastern Cooperative Oncology Group (ECOG) performance status = 0 or 1
  - Life expectancy > 12 weeks
  - Serologically negative for hepatitis B and C virus
  - No prior exposure to fluoropyrimidines and/or irinotecan and/or oxaliplatin
  - No prior treatment with bevacizumab
  - Adequate organ function
  - Adequate bone marrow function
  - Baseline serum creatinine ≤ 1.5 mg/dL
  - Baseline serum bilirubin ≤ 1.5 x ULN
  - Baseline alkaline phosphatase ≤ 3 x ULN
  - Baseline aspartate aminotransferase ≤ 3 x ULN
  - Baseline alanine aminotransferase ≤ 3 x ULN
  - Baseline lactate dehydrogenase ≤ 3 x ULN
  - Baseline serum albumin ≥ 3.0 g/dL
  - Baseline hemoglobin ≥ 10 g/dL

- **Figure 2. SOLSTICE study timeline.**
  - Enrollment ongoing in 25 countries

- **Figure 3. Country (table) is not participating in the SOLSTICE study.**

- **Figure 4. SOLSTICE study site.**
  - SOLSTICE site is not participating in the SOLSTICE study.