O-013 Safety and efficacy of trifluridine/tipiracil in previously treated metastatic colorectal cancer (mCRC): Preliminary results from the phase 3b, international, open-label, early-access PRECONNECT study

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Background

- Trifluridine/tipiracil (FTD/TPI, or TAS-102) is registered in over 48 countries (including Europe, USA and Japan) for the management of patients with metastatic colorectal cancer (mCRC) who had progressed on standard therapies.
- FTD/TPI has a different mechanism of action to 5-fluorouracil (5-FU),[1, 2] and has demonstrated efficacy in mCRC patients refractory to 5-FU.[3]
- In the pivotal phase 3, RECOURSE study (NCT01607957; N=800), FTD/TPI significantly improved overall survival (OS) and progression-free survival (PFS) versus placebo in patients with mCRC who had progressed on standard therapies.[3] In the final survival analysis, median OS with FTD/TPI was 7.2 months versus 5.2 months with placebo (hazard ratio [HR] 0.69; $P<0.0001$).[4]
- The international, phase 3b PRECONNECT early-access study was initiated to provide a large cohort of eligible adult patients with mCRC access to FTD/TPI and to further assess the safety and efficacy of FTD/TPI in daily practice (NCT03306394). Presented herein are the safety and efficacy data of the first 462 patients included and treated in the program up to a cut-off date of 1 November 2017.

Methods

- PRECONNECT is an on-going, open-label, prospective, single-arm study.
- The primary objective of PRECONNECT is to determine the safety of FTD/TPI.
  - Safety was assessed by the incidence of adverse events (AEs), as well as changes in laboratory tests, physical examination, Eastern Cooperative Oncology Group performance status (ECOG PS) and vital signs.
  - ECOG PS deterioration was also assessed and was defined as the time from start of treatment to the first patient ECOG deterioration (changing from an ECOG PS of 0–1 at baseline to ≥2 post baseline).
  - AEs were graded using NCI CTCAE version 4.03.
- The secondary objectives of PRECONNECT include assessment of efficacy of FTD/TPI in terms of investigator-assessed PFS, objective response rate (ORR), and disease control rate (DCR).
- Descriptive statistics are provided, depending on the nature of the variable.

Figure 1. Inclusion criteria, treatment schedule and withdrawal criteria for patients participating in PRECONNECT

- Patients aged ≥18 years with histologically confirmed mCRC
- Receipt of ≥2 prior regimens of standard chemotherapies (fluoropyrimidines, irinotecan, oxalipatin, anti-VEGF MAb, anti-EGFR MAb for KRAS wt)
- Refractory, intolerant or not a candidate for those chemotherapies
- ECOG PS of 0 or 1
- Adequate organ function

↓

FTD/TPI 35 mg/m^2 BID on days 1-5 and 8-12 of each 28-day cycle

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Withdrawal criteria:
- Disease progression
- Unacceptable toxicity
- Withdrawal of consent
- Physician decision
- Pregnancy
- Commercial availability of FTD/TPI

Results: participants and exposure

- Between October 2016 and May 2017, 462 patients from 10 countries were enrolled and received at least one dose of FTD/TPI.

Table 1. Patient demographics, characteristics and previous therapies at baseline.

Characteristic	N=462
Median age, years (range)	64.0 (28–87)
Male	294 (63.6%)
Race	
White	403 (87.2%)
Black or African American	2 (0.4%)
Asian	5 (1.1%)
Other/not reported	52 (11.3%)
ECOG PS* (N=450)	
0	206 (46.0%)
1	243 (54.0%)
Primary tumour site**	
Right colon	113 (24.5%)
Left colon	290 (62.8%)
Not specified	59 (12.7%)
Median time from first metastasis, months (range) (N=460)	32.4 (0–191)
<18 months	88 (19.1%)
≥18 months	372 (80.9%)
Synchronous metastases at diagnosis	240 (51.9%)
RAS status	
Mutant	241 (52.1%)
Wild type	137 (29.7%)
Unknown/not collected***	84 (18.2%)
BRAF status	
Mutant	12 (2.6%)
Wild type	260 (56.3%)
Unknown/not collected	190 (41.1%)
Previous therapies for colorectal cancer (N=460)	
Fluoropyrimidine	459 (99.8%)
Oxaliplatin	452 (98.3%)
Irinotecan	447 (97.2%)
Oxaliplatin + irinotecan	443 (96.3%)
Anti-VEGF	386 (83.9%)
Anti-EGFR	191 (41.5%)
Regorafenib	164 (35.7%)
Other	77 (16.7%)

Values are reported as n (% patients) unless otherwise stated. *1 patient included with ECOG PS 2 at inclusion. **Right colon include transverse location/left colon includes rectum. ***Includes patients with at least one evaluation for KRAS or NRAS status missing, EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor.

Table 2. Patient exposure

	N=462
Duration of treatment, months*	
Mean ± SD	3.6 ± 2.2
Median (range)	3.0 (0.5–11.0)
Median relative dose intensity	89%
Median number of cycles (range)	3 (1–12)
≥3 treatment cycles, n (%)	274 (59.3%)
AEs leading to dose reduction, n (%)	37 (8%)

*Includes time off drug/interruptions.

- At the cut-off for data analysis, 357 (77.3%) patients had withdrawn from the study due to disease progression.
- Of the AEs leading to withdrawal in 31 (6.7%) patients, 10 (2.2%) were treatment-related.

Table 3. Patient withdrawal

	N=462
Ongoing	29 (6.2%)
Reason for study withdrawal	
Progressive disease	357 (77.3%)
Adverse event	31 (6.7%)
Commercial availability/study terminated by sponsor	30 (6.5%)
Physician decision	8 (1.7%)
Withdrawal non-medical reason	6 (1.3%)
Protocol violation	1 (0.2%)

Values are reported as n (% patients).

Results: Safety and efficacy

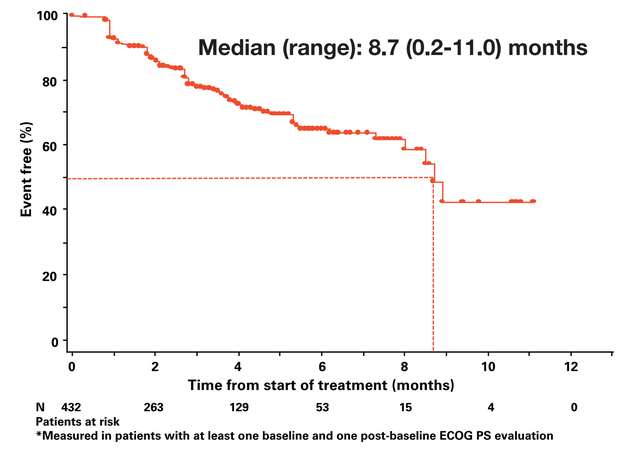
Table 4. Treatment-emergent AEs occurring in >10% of patients and events of interest (N=462).

Treatment-emergent AEs, n (%)	Any grade	Grade ≥3
Any event	428 (92.6%)	335 (72.5%)
Haematological events		
Neutropaenia	237 (51.3%)	182 (39.3%)
Anaemia	130 (28.1%)	55 (11.8%)
Thrombocytopaenia	35 (7.5%)	9 (1.9%)
Febrile neutropaenia	8 (1.7%)	8 (1.7%)
Non-haematological events		
Nausea	145 (31.4%)	5 (1.1%)
Diarrhoea	117 (25.3%)	24 (5.2%)
Fatigue	105 (22.7%)	15 (3.2%)
Asthenia	96 (20.8%)	12 (2.6%)
Vomiting	85 (18.4%)	8 (1.7%)
Decreased appetite	83 (18.0%)	8 (1.7%)
Constipation	58 (12.6%)	2 (<1%)
Cardiac ischaemia*	1 (<1%)	0 (0%)
Liver function		
AST increased	13 (2.8%)	4 (<1%)
ALT increased	12 (2.6%)	1 (<1%)
Renal function		
Increase in creatinine level	2 (<1%)	1 (<1%)

*Events included acute myocardial infarction, angina pectoris, and myocardial ischaemia, ALT, alanine aminotransferase; AST, aspartate aminotransferase.

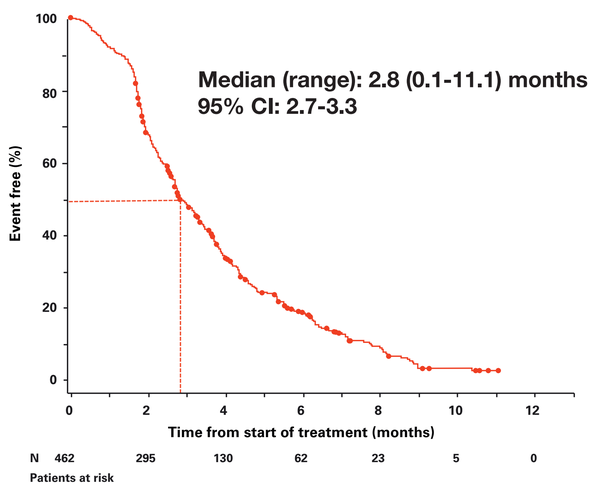
- In PRECONNECT, treatment-emergent AEs regardless of relation to study drug occurred in 92.6% of patients while 72.5% of patients experienced AEs of grade ≥3 severity.
- No new safety signal has been seen to date in the PRECONNECT study.

Figure 2. Kaplan-Meier estimate of ECOG PS deterioration ≥2 (N=432)*



*Measured in patients with at least one baseline and one post-baseline ECOG PS evaluation

Figure 3. Kaplan-Meier estimate of PFS (N=462)



- Investigator-assessed median PFS in the whole population (n=462) was 2.8 months (95% CI 2.7–3.3, range 0.1–11.1). ORR was 2.4% (95% CI 1.2–4.2) and DCR was 36.8% (95% CI 32.4–41.4).
- In a response-evaluable set of 414 patients who received at least one dose of FTD/TPI and had at least one baseline and one post-baseline tumour evaluation, median PFS was 3.2 months (95% CI 2.8–3.4, range 0.1–11.1), ORR 2.7% (95% CI 1.3–4.7) and DCR 41.1% (95% CI 36.3–46.0).

Conclusions

- **Analysis of the safety and efficacy of FTD/TPI in this large interim analysis of the prospective, phase 3b PRECONNECT study in patients with mCRC who have been previously treated with standard therapy demonstrated that:**
  - **The safety profile of FTD/TPI was acceptable and consistent with that reported in the randomized phase 3 RECOURSE trial[3] and other previous randomized trials.[5]**
  - **Median PFS based on investigator assessment was 2.8 months (95% CI 2.7–3.3) compared with 2.0 months (95% CI 1.9–2.1) in RECOURSE treatment arm based on a radiological assessment (N=533).[3]**
  - **DCR was 36,8% compared with 44% in RECOURSE treatment arm (N=533).[3]**
  - **Median time to deterioration of ECOG PS was 8.7 months compared with 5.7 months in RECOURSE treatment arm (N=533).[3]**
- **The PRECONNECT data provide further support of FTD/TPI as a safe and efficacious treatment option for pretreated mCRC patients.**
- **PRECONNECT will also assess the quality of life of patients; preliminary data are anticipated in 2019.**

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