Phase II study evaluating trifluridine/tipiracil + bevacizumab and capecitabine + bevacizumab in first-line unresectable metastatic colorectal cancer (mCRC) patients who are non-eligible for intensive therapy (TASCO1): results of the primary analysis

O-013

Krzysztof Lesniewski-Kmak[1], Vladimir Moiseenko[2], Mark P. Saunders[3], Harpreet Wasan[4], Guillem Argiles[5], Christoph Borg[6], Geert-Jan Creemers[7], Mikhail Fedyanin[8], Robert Glynne-Jones[9], Per Pfeiffer[10], Cornelis J.A. Punt[11], Daniil Stroyakovskiy[12], Albert Ten Tije[13], Agnès J. Van de Wouw[14], Akira Kanehisa[15], Ronan Fougeray[15], Natividad Lopez Busto[15], Nadia Amellal[15], Eric Van Cutsem[16]

[1]Szpitale Wojewodzkie w Gdyni/Gdansk Medical University, Gdynia, Poland; [2]Saint-Petersburg Scientific Practical Center for Specialized Medical Care, St Petersburg, Russia; [3]Christie Hospital NHS Foundation Trust, Manchester, United Kingdom; [4]Hammersmith Hospital, London, UK; [5]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [6]University Hospital Besançon, Besançon, France; [7]Catharina Hospital, Eindhoven, The Netherlands; [8]NN Blokhin National Medical Research Center of Oncology, Moscow, Russia; [9]Mount Vernon Hospital, Northwood, UK; [10]Odense University Hospital, Odense, Denmark; [11]Amsterdam University Medical Centers, Amsterdam, The Netherlands; [12]Moscow City Oncology Hospital N62, Moscow, Russia; [13]Amphia Hospital, Breda, The Netherlands; [14]VieCuri Medisch Centrum Noord-Limburg, Venlo, The Netherlands; [15]Institut de Recherches Internationales Servier, Suresnes, France; [16]University Hospitals Leuven and KU Leuven, Leuven, Belgium.

Background

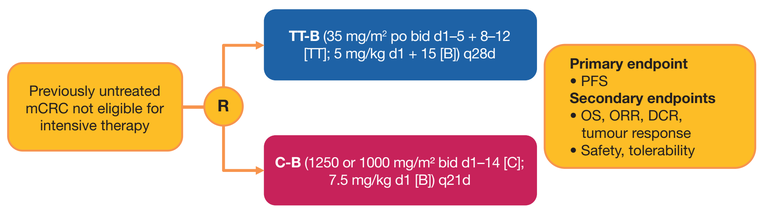
- Trifluridine/tipiracil (TT), also known as TAS-102, is a novel chemotherapy approved in patients with metastatic colorectal cancer (mCRC) refractory or not candidate to standard therapies.[1] It is an oral combination of the antineoplastic, thymidine-based nucleoside analogue trifluridine (FTD) and the thymidine phosphorylase inhibitor tipiracil hydrochloride (TPI) at a molar ratio of 1:0.5.[2, 3] FTD is incorporated into DNA causing DNA dysfunction,[3, 4] while TPI improves the bioavailability of FTD.[2, 3, 5]
- Bevacizumab (B) is a recombinant humanized monoclonal antibody that inhibits angiogenesis and may normalise tumour vasculature, thereby improving tumour blood supply.[6] Due to its mechanism of action, it was thought that adding B to TT would increase the accumulation of trifluridine and its subsequent phosphorylation in tumours.
- Combining TT with bevacizumab increases trifluridine concentrations in tumoral DNA without increasing systemic trifluridine exposure. This may help minimise systemic toxicity while optimising antitumour activity.[6]
- The phase I/II C-TASK FORCE study evaluated the combination of TT-B in advanced mCRC patients who were refractory to standard therapies; results suggested encouraging antitumour activity with manageable toxicity.[6]
- TASCO1 was initiated to evaluate the efficacy and safety TT-B as first-line treatment in patients with unresectable mCRC who were non-eligible for intensive therapy.

Methods

Study design and treatment

- TASCO1 (ClinicalTrials.gov number: NCT02743221) was a multicentre, randomized, open-label, phase 2 trial (Figure 1).
- Eligible patients were first-line mCRC patients not candidate for intensive oxaliplatin- or irinotecan-based chemotherapy or without chance for curative resection according to the investigator's judgment.
- Patients were randomized in a 1:1 ratio, stratified by RAS status, Eastern Cooperative Oncology Group performance status (ECOG PS) and country. Treatment was continued until disease progression, intolerant toxicity or patient refusal.

Figure 1. Study design.



B, bevacizumab; bid, twice daily; C, capecitabine; d, day; DCR, disease control rate; mCRC, metastatic colorectal cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; po, oral; qXd, every X days; R, randomised; TT, trifluridine/tipiracil.

- The primary endpoint was progression-free survival (PFS), based on investigator assessment of radiologic images, per RECIST 1.1 criteria.
- Secondary endpoints included overall survival (OS), tumour response, including objective response rate (ORR) and disease control rate (DCR), assessed a minimum of 6 weeks after start of treatment, and safety and tolerability.
- Quality of life and biomarker data from the trial were also assessed and will be presented elsewhere.

Results

- Between April 29, 2016 and March 29, 2017, 154 patients from 52 sites in 12 countries were randomized and 153 patients were treated. Baseline characteristics were well balanced (Table 1).

Results

Table 1. Patient baseline demographics and characteristics.

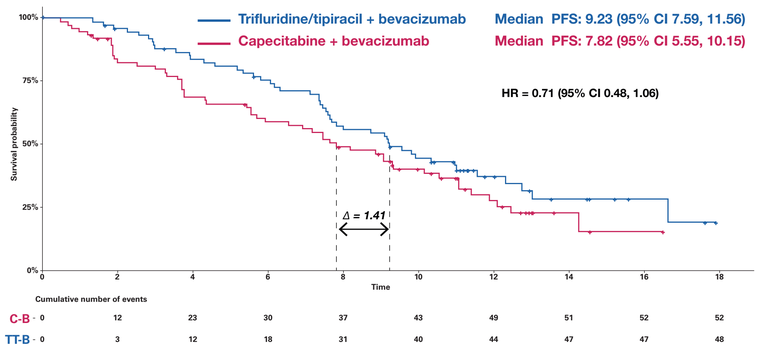
Characteristic	TT-B (N=77)	C-B (N=76)
Median age, years (range)	73 (64–77)	75.5 (67–81)
Gender		
Male	51.9%	61.8%
Female	48.1%	38.2%
ECOG PS		
0	33.8%	34.2%
1	49.3%	51.3%
2	16.9%	14.5%
Primary tumour site		
Right colon	39.0%	25.0%
Left colon	61.0%	75.0%
Prior adjuvant therapy		
Yes	27.3%	19.7%
No	72.7%	80.3%
RAS mutational status		
Mutant	57.1%	56.6%
Wild type	42.9%	43.4%
BRAF mutational status		
Mutant	10.4%	9.2%
Wild type	67.5%	71.1%
Unknown/not collected	22.1%	19.7%

Values are reported as % patients unless otherwise stated. B, bevacizumab; C, capecitabine; ECOG PS, Eastern Cooperative Oncology Group performance status; TT, trifluridine/tipiracil.

Efficacy

- Median PFS was 9.2 months with TT-B and 7.8 months with C-B giving a hazard ratio (HR) of 0.71 (95% confidence interval [CI] 0.48, 1.06) for TT-B versus C-B (Figure 2).

Figure 2. Kaplan-Meier estimates of PFS.



CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

- A positive trend for prolonged PFS with TT-B versus C-B in all prespecified subgroups (Table 2).

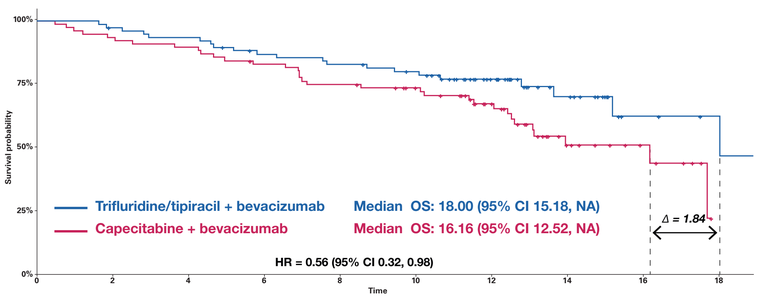
Table 2. PFS subgroup analyses.

Variable	Subgroup	HR (95% CI)	HR (95% CI)
RAS status	Mutant		0.59 (0.35, 0.98)
	Wild		1.04 (0.55, 1.95)
ECOG PS	0		0.76 (0.33, 1.73)
	1		0.69 (0.41, 1.16)
	2		0.83 (0.35, 2.01)
Gender	Female		0.5 (0.28, 0.89)
	Male		0.89 (0.51, 1.54)
Age	65–75		0.86 (0.4, 1.84)
	≤65		0.46 (0.21, 1.01)
	>75		0.84 (0.45; 1.56)
Age 65	≤65		0.46 (0.21, 1.01)
	>65		0.82 (0.51, 1.31)
Age 75	≤75		0.68 (0.4,1.15)
	>75		0.84 (0.45, 1.56)
Region	Europe		0.73 (0.47, 1.14)
	Outside Europe		0.81 (0.32, 2.06)
Prior adjuvant treatment	No		0.69 (0.44, 1.08)
	Yes		1.14 (0.48, 2.7)
Primary tumour site	Left colon		0.5 (0.31, 0.82)
	Right colon		1.64 (0.77, 3.5)
Surgery resection	No		0.35 (0.16, 0.74)
	Yes		1.02 (0.64, 1.64)
Number of met sites	≥3		0.73 (0.46, 1.16)
	1–2		0.76 (0.35, 1.65)
Presence of liver met	No		0.55 (0.26, 1.17)
	Yes		0.86 (0.54, 1.38)
BRAF status	Mutant		0.37 (0.11, 1.25)
	Not done		0.68 (0.31, 1.51)
	Wild		0.85 (0.52, 1.4)
Time since met diagnosis	≤4		0.7 (0.45, 1.08)
	>4		1.19 (0.43, 3.27)
Summary			

Results

- Preliminary median OS was 18 months with TT-B and 16.2 months with C-B giving a HR of 0.56 (95% CI 0.32, 0.98) for TT-B versus C-B (Figure 3).

Figure 3. Kaplan-Meier estimates of OS.



CI, confidence interval; HR, hazard ratio; NA, not available; OS, overall survival.

- DCR was higher with TT-B versus C-B (Table 3).

Table 3. Response to treatment.

Response	TT-B (N=77)	C-B (N=76)
ORR	26 (33.8%)	23 (30.3%)
95% CI	23.4%, 45.5%	20.3%, 41.9%
DCR	66 (85.7%)	59 (77.6%)
95% CI	75.9%, 92.7%	66.6%, 86.4%
Best overall response		
PR	26 (33.8%)	23 (30.3%)
SD	40 (52.0%)	36 (47.4%)
PD	4 (5.2%)	12 (15.8%)
NE	7 (9.1%)	5 (6.6%)

Values are reported as n (% patients) unless otherwise stated. B, bevacizumab; C, capecitabine; CI, confidence interval; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TT, trifluridine/tipiracil.

Safety

- In TASCO1, serious treatment-emergent AEs occurred in 54.5% of patients receiving TT-B and 57.9% of patients receiving C-B (Tables 4 and 5). Serious febrile neutropenia occurred in 3.9% of patients receiving TT-B, identical to the rate of patients receiving C-B.

Table 4. Non-haematological AEs occurring in >10% of patients.

Non-haematological AEs, %	TT-B (N=77)			C-B (N=76)		
	Any grade	Grade 3	Grade 4	Any grade	Grade ≥3	Grade 4
Diarrhoea	53.2%	1.3%	–	43.4%	6.6%	–
Nausea	46.8%	2.6%	–	18.4%	–	–
Vomiting	28.6%	5.2%	–	11.8%	1.3%	–
Constipation	16.9%	–	–	19.7%	–	–
Abdominal pain	11.7%	1.3%	–	7.9%	1.3%	–
Decreased appetite	37.7%	–	–	19.7%	1.3%	–
Weight decreased	11.7%	1.3%	–	7.9%	1.3%	–
Stomatitis	16.9%	1.3%	–	21.1%	–	–
Hand-foot syndrome	3.9%	–	–	52.6%	11.8%	–
Alopecia	22.1%	–	–	–	–	–
Fatigue	36.4%	3.9%	–	30.3%	3.9%	–
Asthenia	18.2%	5.2%	–	22.4%	2.6%	–
Viral URTI	10.4%	–	–	6.6%	–	–
Dysgeusia	9.1%	–	–	10.5%	–	–
Dizziness	6.5%	–	–	10.5%	–	–
Dyspnoea	7.8%	–	–	10.5%	1.3%	–
Hypertension	15.6%	13.0%	–	13.2%	3.9%	1.3%
Malignant neoplasm progression	19.5%	3.9%	7.8%*	23.7%	3.9%	15.8%

AEs, adverse events; B, bevacizumab; C, capecitabine; TT, trifluridine/tipiracil; URTI, upper respiratory tract infection. *Gr. 5; 7.8% in TT-B and 15.8% in C-B.

Table 5. Hematological toxicities (as treated population).

Lab abnormalities, %	TT-B (N=77)			C-B (N=76)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Hematology						
Anemia, %	31.2	9.1	1.3	6.6	-	-
Neutropenia, %	53.2	22.1	24.7	6.6	2.6	2.6
Neutrophil count decrease, %	23.4	14.3	3.9	2.6	-	1.3
Leukopenia, %	7.8	3.9	-	2.6	1.3	-
White blood cell count decrease, %	19.5	10.4	-	2.6	1.3	1.3
Thrombocytopenia, %	14.3	3.9	-	5.3	1.3	-
Febrile neutropenia,%	5.2	2.6	2.6	3.9	2.6	1.3
Serious febrile neutropenia,%		3.9%			3.9%	

Conclusions

- **Primary analysis of the efficacy and safety of TT-B in patients with mCRC not eligible for intensive therapy in the multicentre, randomised, open-label, phase 2 TASCO1 trial showed a median PFS of 9.2 months with TT-B and 7.8 months with C-B, supporting the promising activity of this combination observed in C-TASK FORCE. [6] This trend in efficacy in PFS was observed across all stratification factors and most predefined subgroups.**
- **Preliminary OS follows a consistent trend with PFS.**
- **The safety profile of TT-B was found to be acceptable, with comparable rates of haematological toxicities as in C-TASK FORCE,[6] more gastrointestinal toxicities and a much lower rate of hand-foot syndrome than C-B.**
- **The opportunity to conduct a global confirmatory phase 3 trial versus C-B is currently being evaluated.**

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For any queries related to information found on this poster please contact Eric Van Cutsem (eric.vancutsem@uzleuven.be).

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