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ORIGINAL ARTICLE

Trifluridine/tipiracil plus bevacizumab in patients with untreated metastatic colorectal cancer ineligible for intensive therapy: the randomized TASCO1 study☆

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Background: We designed an open-label, noncomparative phase II study to assess the safety and efficacy of first-line treatment with trifluridine/tipiracil plus bevacizumab (TT—B) and capecitabine plus bevacizumab (C—B) in untreated patients with unresectable metastatic colorectal cancer (mCRC) who were not candidates for combination with cytotoxic chemotherapies.

Patients and methods: From 29 April 2016 to 29 March 2017, 153 patients were randomly assigned (1:1) to either TT—B ($N = 77$) or C—B ($N = 76$). The primary end point was progression-free survival (PFS). The primary PFS analysis was performed after 100 events (radiological progression or death) were observed. Secondary end points included overall survival (OS), quality of life (QoL; QLQ-C30 and QLQ-CR29 questionnaires), and safety.

Results: Median (range) duration of treatment was 7.8 (6.0—9.7) months and 6.2 (4.1—9.1) months in the TT—B and C—B groups, respectively. Median (range) PFS was 9.2 (7.6—11.6) and 7.8 (5.5—10.1) months, respectively. Median (range) OS was 18 (15.2 to NA) and 16.2 (12.5 to NA) months, respectively. QoL questionnaires showed no relevant changes over time for either treatment. Therapies were well tolerated. Patients receiving TT—B had more grade ≥3 neutropenia (47% versus 5% with C—B). Patients receiving C—B had more grade ≥3 hand—foot syndrome (12% versus 0% with TT—B) and grade ≥3 diarrhea (8% versus 1% with TT—B), consistent with the known safety profiles of these agents.

Conclusion: TT—B treatment showed promising clinical activity in untreated patients with unresectable mCRC ineligible for intensive therapy, with an acceptable safety profile and no clinically relevant changes in QoL.

Clinical trial information: NCT02743221 (ClinicalTrials.gov)

Key words: bevacizumab, capecitabine, intensive therapy, metastatic colorectal cancer, TASCO1 study, trifluridine/tipiracil

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☆ Note: This study was previously presented as follows:

- Lesniewski-Kmak K, Moiseenko V, Saunders M, et al. 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. *Ann Oncol.* 2018;29(Suppl. 5):O-022. Oral presentation by E. Van Cutsem.
- Moiseenko V, Lesniewski-Kmak K, Saunders MP, et al. Design of a phase II study evaluating trifluridine/tipiracil+bevacizumab and capecitabine+bevacizumab for first-line treatment of patients with unresectable metastatic colorectal cancer (mCRC) who are non-eligible for intensive therapy (TASCO1). *Ann Oncol.* 2017;28(Suppl. 3):Poster 353.
- Moiseyenko V, Saunders MP, Wasan HS, et al. QoL from TASCO1: health related quality of life of trifluridine/tipiracil-bevacizumab and capecitabine-bevacizumab as first-line treatments in metastatic colorectal cancer patients not eligible for intensive chemotherapy: results from the TASCO1 phase 2 study. *J Clin Oncol.* 2019;37(Suppl. 4):Abstract 676.

INTRODUCTION

The recommended first-line treatment for metastatic colorectal cancer (mCRC) includes the combination of cytotoxic drugs such as oxaliplatin, irinotecan, and fluoropyrimidines with biological targeted agents (e.g. bevacizumab, cetuximab, and panitumumab).[1] Treatment options are more limited for patients ineligible for such intensive chemotherapies, hence there is currently an unmet medical need. For these patients, the therapy goal is to prevent tumor progression and prolong survival without compromising quality of life (QoL). Thus, the recommended first-line therapy in these cases is a fluoropyrimidine (e.g. capecitabine) with or without bevacizumab.[1]

Trifluridine/tipiracil (also known as TAS-102 or FTD/TPI) is an approved oral treatment for patients with advanced mCRC. It combines an antineoplastic thymidine-based nucleoside analog (trifluridine) and a thymidine phosphorylase inhibitor (tipiracil hydrochloride).[2] Previous studies, including the phase III RECOURSE trial, showed that third-line treatment with trifluridine/tipiracil significantly improved progression-free survival (PFS) and overall survival (OS) in patients with mCRC who were refractory or intolerant to standard therapies.[3–5] Notably, these results were observed across different patient subgroups, regardless of age, geographical origin, or *KRAS* gene mutation status.[6] Trifluridine/tipiracil was well tolerated, presented a good and manageable safety profile,[3,4] and did not appear to negatively impact patient QoL.[7]

The clinical benefit associated with trifluridine/tipiracil has led to exploration of potential combination regimens with other agents in mCRC.[2] One such agent is the antivascular endothelial growth factor antibody bevacizumab, which improves PFS when added to first-line chemotherapy with other agents.[8–10] Preclinical studies in mouse xenografts have shown that trifluridine/tipiracil plus bevacizumab (TT—B) significantly reduces tumor growth compared with either treatment alone.[11] Moreover, clinical data from the phase I/II C-TASK FORCE study showed that treatment with TT—B induced promising antitumor activity with manageable toxicity in a small patient population with advanced mCRC refractory or intolerant to standard therapies.[12]

We therefore conducted the randomized phase II TASCO1 (TAS-102 in COlorectal cancer) study to evaluate the efficacy and safety of TT—B in patients with unresectable mCRC ineligible for intensive oxaliplatin- or irinotecan-based chemotherapy. This noncomparative study included capecitabine plus bevacizumab (C—B) as reference treatment for the same population. This is the first trial of trifluridine/tipiracil as a first-line therapy in mCRC.

PATIENTS AND METHODS

Participants

Eligible patients were men or women aged ≥18 years with unresectable mCRC diagnosed within 6 months prior to the start of study treatment. Patients had histological or cytological confirmation of colorectal adenocarcinoma, with available *RAS* mutation status (and *BRAF* status, if available) determined by tumor biopsy, and at least one measurable metastatic lesion, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[13] and Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2. Patients should not have received previous systemic anticancer therapy for unresectable mCRC and, according to investigator's judgment, were not candidates for full-dose combination chemotherapy with irinotecan or oxaliplatin or for curative resection of metastatic lesions. Previous adjuvant (or neoadjuvant) chemotherapy was allowed only if completed more than 6 months prior to start of study treatment. Key exclusion criteria included history of other serious illnesses, major surgery, radiation therapy, or treatment with an investigational agent within 4 weeks prior to randomization or allergy to any of the study treatments or its excipients.

Study design and treatment

TASCO1 was a multinational, open-label, randomized, noncomparative phase II study conducted in 52 hospital centers across 12 countries (Australia, Belgium, Brazil, Denmark, France, Germany, Italy, The Netherlands, Poland, Russia, Spain, and UK). The study was reviewed and approved by the Institutional Review Board at each participating center and performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent. An independent data safety monitoring board provided frequent oversight of the study. This study was registered with ClinicalTrials.gov (registration number NCT02743221). The final study protocol is available online.

Eligible patients were randomly assigned by the minimization procedure in a 1:1 ratio via an interactive web-response system to receive either TT—B or C—B (reference therapy). Randomization was stratified by *RAS* status, ECOG PS, and country. Study treatment was not blinded to patients or to the investigators.

Patients assigned to TT—B received trifluridine/tipiracil (35 mg/m^2/dose) orally twice daily, 5 days a week (plus 2 days of rest) for 2 weeks, followed by a 14-day rest period, thus completing one treatment cycle. Bevacizumab (5 mg/kg) was administered intravenously every 2 weeks (on days 1 and 15 of each cycle). Patients assigned to C—B received capecitabine (1250 mg/m^2) orally twice daily (days 1—14 of each cycle), followed by a 7-day rest period, with bevacizumab (7.5 mg/kg) administered intravenously on day 1 of each cycle. The TT—B dosing regimen was repeated every 4 weeks and the C—B regimen every 3 weeks. Cycles were repeated until disease progression, unacceptable toxicity, investigator's/patient's decision, or death. Hematologic support including blood transfusions, granulocyte colony-stimulating factor, and erythropoietin was allowed by the study protocol.

End points and assessments

The primary end point was PFS, defined as the time from randomization to radiological disease progression, or death due to any cause. Secondary end points included OS (time in

months from randomization to death from any cause), overall response rate (ORR; proportion of patients with objective evidence of confirmed complete response or partial response as best overall response), disease control rate (DCR; proportion of patients with objective evidence of confirmed complete response, partial response, or stable disease as best overall response), duration of response (DR), QoL measures, and safety.

Tumor assessments based on RECIST version 1.1[13] were performed every 8 weeks until progression, death, or initiation of a new anticancer treatment. QoL was assessed using the European Organization for Research and Treatment of Cancer QLQ-C30 and CRC-specific QLQ-CR29 questionnaires at baseline and every 12 weeks thereafter until discontinuation. Adverse events (AEs) were recorded throughout the study and assessed by the investigator according to seriousness, severity (National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0),[14] and causal relationship to study treatments.

Statistical analysis

Sample size is based on estimating the PFS hazard ratio (HR) with certain precision in order to optimize a future phase 3 confirmatory design. The primary PFS analysis was conducted after 100 events (radiological progression or death) were collected. With an anticipated median PFS of 9 months in the C—B group, and study recruitment period of ∼24 months and an expected HR of 0.77 with a two-sided 80% confidence interval, a sample size of 150 patients was deemed necessary to obtain 100 PFS events over ∼12 months after the last patient randomized.

The full analysis set used for PFS and OS analyses consisted of all randomized patients who received at least one intake of study drug. Patients were analyzed based on their initial randomized group. HRs and the corresponding two-tailed 80% and 95% confidence intervals (CIs) between groups were calculated using a Cox proportional hazards model adjusted on *RAS* status and ECOG PS. Associated Kaplan—Meier survival estimates were summarized for both groups.

Secondary subgroup analyses were performed on prespecified factors. An adjusted multivariate Cox regression analysis was used to investigate the effect of prespecified potential prognostic/predictive factors on PFS. DCR and ORR were compared using the Fisher's exact test with two-tailed 95% Clopper Pearson CIs with the intention-to-treat principle. DR was analyzed according to the per-protocol principle for patients with measurable disease at baseline, at least one tumor evaluation on treatment, and presenting a tumor response. For QoL scores analyses, clinically relevant change from baseline was considered for difference of ±10 points.

Statistical analyses were performed using SAS (version 9.2; SAS Institute, Cary, NC).

RESULTS

Patient disposition and baseline characteristics

Between 29 April 2016 and 29 March 2017, 154 treatment-naïve patients with unresectable mCRC were randomly assigned to receive either TT—B ($n = 77$) or C—B ($n = 76$) treatment. One patient was randomized but not treated. Details of patient disposition are shown in Figure 1.

Baseline characteristics were generally well balanced between treatment groups (Table 1). Overall, median age was 75 years (range 33—91) and 43% of patients were female. Most patients had three or more metastatic sites (73%) and most had not received prior adjuvant therapy (76%). Half of the patients had ECOG PS 1 and 16% had ECOG PS 2.

Median (range) duration of treatment was 7.8 (6.0—9.7) months and 6.2 (4.1—9.1) months in the TT—B and C—B groups, respectively. The main reasons for ineligibility to intensive therapy according to investigator judgment are listed in Table 1.

Efficacy

At the PFS cut-off date (15 January 2018), the 100 PFS events had been observed in 48 patients (62%) in the TT—B group and 52 patients (68%) in the C—B group. Median (range) PFS was 9.2 (7.6—11.6) and 7.8 (5.5—10.1) months, respectively (Figure 2A). At 12 months after baseline, the PFS rate was 40% in the TT—B group and 30% in the C—B group. At the OS cut-off date (20 January 2018), 22 patients (29%) in the TT—B group and 33 patients (43%) in the C—B group had died. Median (range) OS followed a trend consistent with PFS results: 18 (15.2 to NA) and 16.2 (12.5 to NA) months, respectively (Figure 2B).

Table 2 summarizes tumor responses in randomized and treated patients. In terms of best overall response, partial responses were confirmed in 26 patients (34%) in the TT—B group and in 23 patients (30%) in the C—B group. ORR was similar in both treatment groups (34% and 30% for TT—B and C—B, respectively), although the DCR was higher in patients in the TT—B group (86% and 78%, respectively). Median (range) DR was 7.9 (5.5—16.6) months in the TT—B group and 9.9 (7.0 to NA) months in the C—B group. This analysis of DR was conducted on 48 patients (31% of the full analysis set population) and cannot be considered robust.

For most of the stratification factors and predefined subgroups, the treatment effect on PFS was in favor of the TT—B group and more particularly in women and patients with *RAS* mutations, disease located in the left colon, or an absence of surgical resection (Figure 3).

Safety

Almost all patients experienced at least one AE of any grade. Overall, AEs of grade ≥3 occurred more frequently in the TT—B group compared with the C—B group (88% versus 70%). Most patients had at least one treatment cycle delayed (79% in the TT—B group versus 74% in the C—B group). Most cycles were delayed due to medical reasons. The percentage of patients who had at least one cycle with dose reduced was 40% in the TT—B group versus 49% in the C—B group. Treatment-related emerging AEs leading to

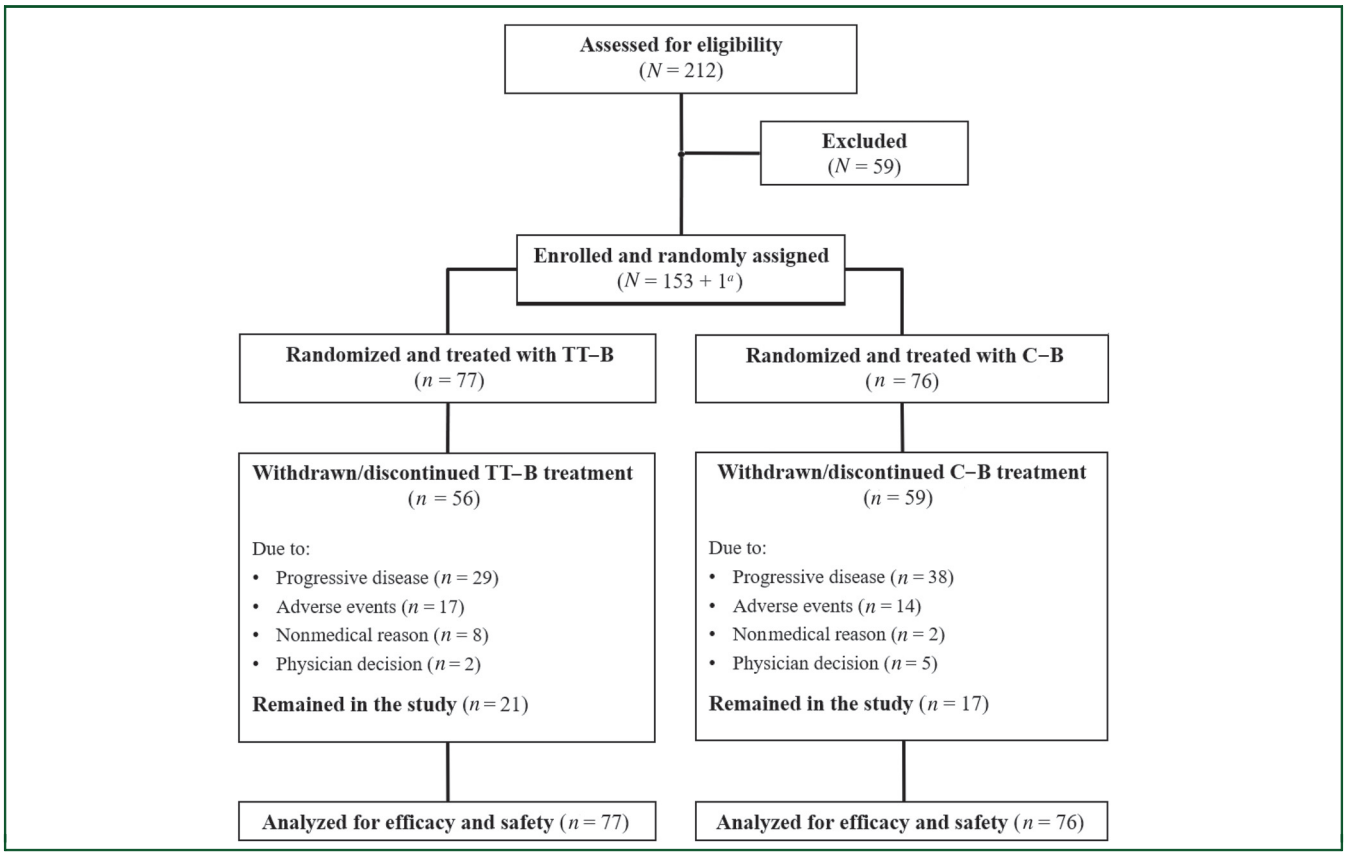

Figure 1. CONSORT diagram.
Excluded were patients with screen failures or who withdrew. C—B, capecitabine plus bevacizumab; TT—B, trifluridine/tipiracil plus bevacizumab.
[a] One patient was randomized but did not receive any study drug.

treatment withdrawal were reported with similar frequency: 14 patients (18%) in the TT—B group and in 11 patients (14%) in the C—B group.

Table 3 presents the most frequent AEs in each group. The frequency of neutropenia of grade ≥3 was higher in the TT—B group than in the C—B group (47% versus 5%), as was the frequency of other grade ≥3 hematological events such as decreased neutrophil count (18% versus 1%), anemia (10% versus 0%), and decreased white blood cell count (10% versus 3%). Grade ≥3 febrile neutropenia events occurred in 5% and 4% of patients in the TT—B and C—B groups, respectively. Patients treated with TT—B also experienced more grade ≥3 events of nausea (3% versus 0%), vomiting (5% versus 1%), and hypertension (13% versus 5%). Compared with the TT—B group, the C—B group presented a higher frequency of grade ≥3 hand—foot syndrome (12% versus 0%) and diarrhea (8% versus 1%). Four deaths were considered related to treatment including intestinal perforation related to bevacizumab (two patients in the TT—B group), renal failure related to capecitabine (one patient), and Stevens—Johnson syndrome related to capecitabine and bevacizumab (one patient).

Quality of life

The QLQ-C30 questionnaire showed no clinically relevant changes from baseline in the global health status and functioning scales and most symptom scales (mean ± standard deviation), except for nausea/vomiting [TT—B versus C—B; worsening (12 ± 21.2) and no change (−6.4 ± 18.7)], diarrhea [worsening (14.8 ± 30.7) and no change (−7.1 ± 37.4)], fatigue [no change (6.1 ± 21.5) and worsening (16.3 ± 18.2)], loss of appetite [worsening in both groups (13.6 ± 19.7 and 10.5 ± 27.3)], and insomnia [improvement in both groups (−12.1 ± 28.3 and −13.3 ± 35.2)].

The QLQ-CR29 questionnaire showed no clinically relevant change in function score in either treatment group from baseline or between treatments. Most items presented no clinically relevant change from baseline, except for hair loss [worsening for TT—B (28.9 ± 36.9) versus no change for C—B (0.0 ± 18.5)], trouble with taste [improvement (33.3 ± 28.2) and worsening (−11.1 ± 29.6)], sore skin [no change (−3.9 ± 27.2) and worsening (14.3 ± 17.1)], dry mouth [no change (−1.7 ± 22.9) and worsening (15.0 ± 36.6)], and anxiety [no change (4.4 ± 24.8) and improvement (18.0 ± 29.2)].

DISCUSSION

In this phase II study, in randomized settings, we evaluated the efficacy and safety of TT—B in patients with previously untreated unresectable mCRC who were ineligible to receive intensive standard chemotherapy regimens. To our knowledge, this is the first study that has ever been conducted in this population, and due to the absence of an

Table 1. Baseline characteristics of randomized patients

	TT—B treatment (*N* = 77)	C—B treatment (*N* = 76)	All patients (*N* = 153)
Median age (range), years	73.0 (43.0—83.0)	75.5 (33.0—91.0)	75.0 (33.0—91.0)
≤65 years	21 (27)	18 (24)	39 (25)
>65—75 years	28 (36)	20 (26)	48 (31)
>75 years	28 (36)	38 (50)	66 (43)
Male	40 (52)	48 (62)	88 (57)
Ethnic origin[a]			
White	73 (98)	71 (96)	144 (97)
Asian	1 (1)	2 (3)	3 (2)
Other	1 (1)	1 (1)	2 (1)
ECOG PS			
0	26 (34)	26 (34)	52 (34)
1	38 (49)	39 (51)	77 (50)
2	13 (17)	11 (15)	24 (16)
RAS status			
Mutant type	44 (57)	43 (57)	87 (57)
Wild type	33 (43)	33 (43)	66 (43)
Primary tumor site			
Right colon	30 (39)	19 (25)	49 (32)
Left colon	47 (61)	57 (75)	104 (68)
Number of metastatic sites			
1 or 2 sites	20 (26)	22 (29)	42 (27)
≥3 sites	57 (74)	54 (71)	111 (73)
Prior adjuvant therapy			
Yes	21 (27)	15 (20)	36 (24)
No	56 (73)	61 (80)	117 (76)
BRAF mutation status			
Mutant	8 (10)	7 (9)	15 (10)
Wild type	52 (68)	53 (70)	105 (69)
Not done	17 (22)	16 (21)	33 (22)
Reasons for ineligibility to intensive treatment			
Elderly	28 (36)	42 (55)	70 (46)
Tumor burden	15 (20)	14 (18)	29 (19)
ECOG PS	14 (18)	2 (3)	16 (10)
Comorbidities	7 (9)	3 (4)	10 (7)
Other	13 (17)	15 (20)	28 (18)

Data are presented as number of patients (%), unless otherwise indicated, as of 20 January 2018 (overall survival cut-off date).
C—B, capecitabine plus bevacizumab; ECOG PS, Eastern Cooperative Oncology Group performance status; TT—B, trifluridine/tipiracil plus bevacizumab.
[a] Not recorded in two patients in each group.

approved standard therapy we designed this study not to test any statistical hypothesis but to collect essential clinical data to plan further research.

We chose C—B as a reference regimen based on the results of the AVEX trial.[8] This multicenter phase III study compared capecitabine with C—B in elderly patients (aged ≥70 years) with previously untreated mCRC, not candidates for oxaliplatin- or irinotecan-based chemotherapies. While designing this study, we faced with a challenge to introduce the criteria which will define the population of patients ineligible to intensive chemotherapy. We found out that such criteria have not yet been summarized in any existing guideline or recommendation. At the same time, according to the literature, in routine practice only 40%—50% of patients will fall into the category of being eligible to intensive chemotherapy and up to one-third of patients are not treated with standard chemotherapy options while being deemed eligible to receive chemotherapy by an oncologist.[15,16]

Therefore in our study we instructed investigators to select the primary reason for ineligibility to intensive chemotherapy within the following five categories: age, comorbidities, low tumor burden, PS, and other reasons. We believed that this range of categories was adequate to allow enrolment of a broader population not only limited to elderly people.

Analysis of the patient's baseline characteristics showed a balanced distribution between two treatment arms and provided an important evidence about the main reasons for ineligibility to intensive chemotherapy. Notably, in 54% of the study population the primary reason for ineligibility to intensive chemotherapy was not related to age which proves that our endeavor was reasonable in defining this population, and further search of best treatment options is warranted.

The outcome of the primary end point provided a considerable evidence for TT—B as an effective regiment in first-line mCRC. A median (range) PFS of 9.2 (6.0—9.7) months was observed in the TT—B group and of 7.8 (4.1—9.1) months in the C—B group. PFS rate at 12 months was 40% in the TT—B group and 30% in the C—B group. Although OS data are not yet mature, promising OS results were observed consistently with the PFS. Results for other efficacy end points were generally similar between groups, although DCR was numerically higher in the TT—B group.

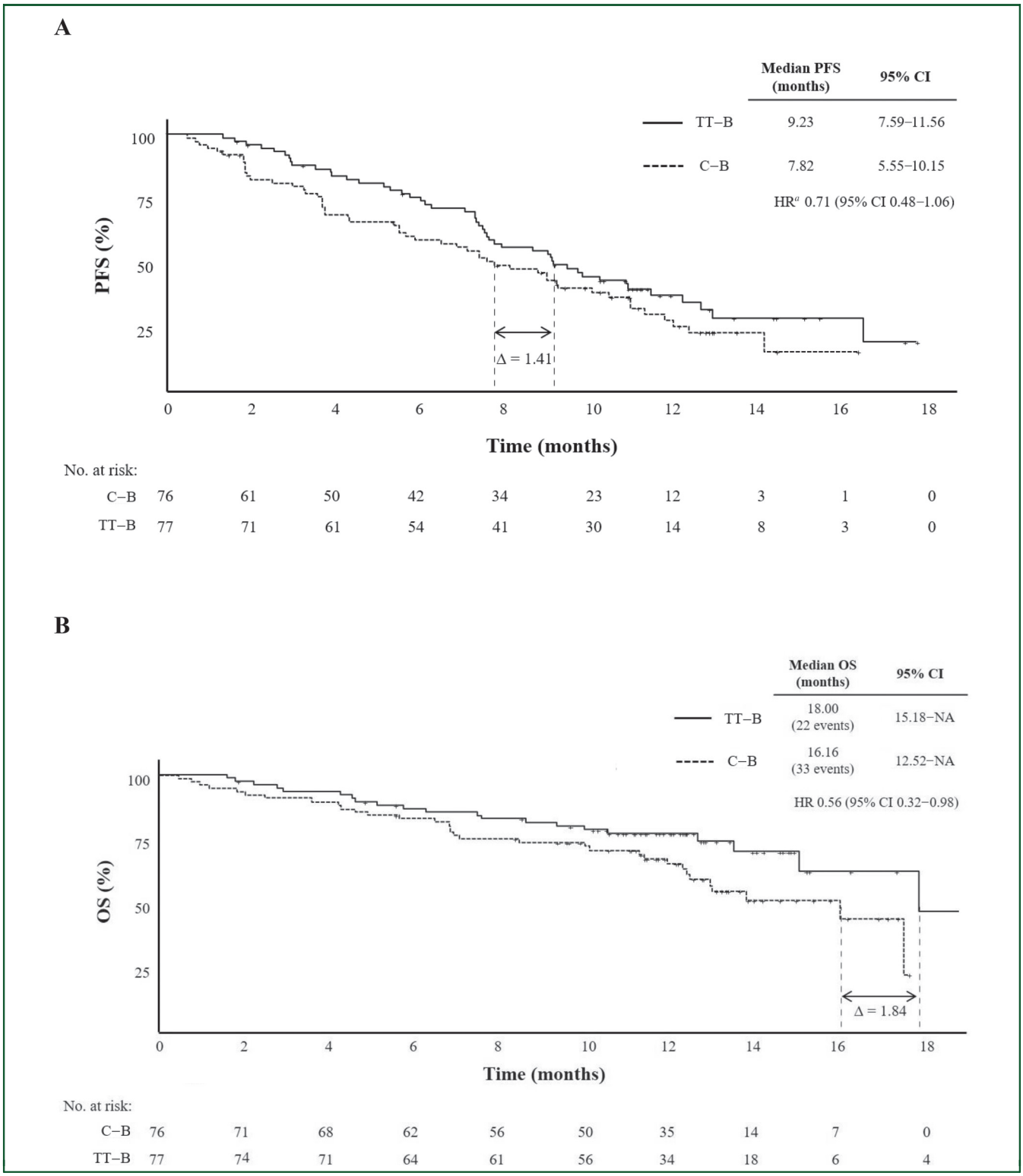

Figure 2. Kaplan–Meier curves for (A) progression-free survival (PFS) and (B) overall survival (OS).
C–B, capecitabine plus bevacizumab; CI, confidence interval; HR, hazard ratio; TT–B, trifluridine/tipiracil plus bevacizumab. Δ indicates difference between the two medians.
[a] Adjusted on stratification covariates. The hazard ratio and its confidence interval are presented for information only.

An indirect comparison between efficacy outcomes from our study with the AVEX study shows that the median PFS and OS in the C–B group of TASCO1 were slightly lower than those reported in AVEX (7.8 versus 9.1 months for PFS, 16.2 versus 21 months for OS).[8] Conceivably, these differences may be explained by the fact that our study was targeting different population of patients. Although the AVEX study was designed for elderly patients, the median

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Table 2. Tumor response in randomized and treated patients

	TT—B treatment (*N* = 77)	C—B treatment (*N* = 76)
Best overall response		
Partial response	26 (34)	23 (30)
Stable disease	40 (52)	36 (47)
Progressive disease	4 (5)	12 (16)
Not evaluable	7 (9)	5 (7)
Overall response rate	26 (34)	23 (30)
Disease control rate	66 (86)	59 (78)

Data are number (%) of patients as of 20 January 2018 (overall survival cutoff date).
C—B, capecitabine plus bevacizumab; TT—B, trifluridine/tipiracil plus bevacizumab.

age was 76 years while in TASCO1 it was 75 years. Nevertheless, there was a higher proportion of patients with EGOG PS2 in TASCO1 (15%) compared with AVEX (7%).

Overall, the therapy with either TT—B or C—B was well tolerated and the safety profiles of each regimen were consistent with those reported by other studies.[8,12,17] No new safety signals were identified. Importantly treatment-related emerging AEs leading to treatment withdrawal were reported with similar frequency: 14 patients (18%) in the TT—B group and in 11 patients (14%) in the C—B.

Analysis of QoL questionnaires showed no relevant changes over time, indicating that neither treatment worsened patient QoL.

Several limitations are worth noting for our study. The foremost in the row was certainly the definition of criteria for selection of noncandidates for standard chemotherapy regimens. Another limitation was the absence of an independent review to assess PFS to confirm the results on the primary end point. Study eligibility criteria allowed inclusion of a heterogeneous population, which may have had an impact on the outcomes. The heterogeneity of the study population may have also hindered the identification of a patient's subgroup who benefited more from TT—B. Finally, the OS data are immature at this stage and updated OS results will be published soon.

Our study was the first to evaluate the TT—B combination as a potential first-line treatment for advanced mCRC. Clinical trials are now underway to further evaluate the effect of the TT—B combination in refractory mCRC as second-line treatment.[18] In addition, a randomized phase II study recently showed that therapy with TT—B, as compared with trifluridine/tipiracil monotherapy, was associated with a significant and clinically relevant improvement in PFS and OS in patients with chemo-refractory mCRC.[19]

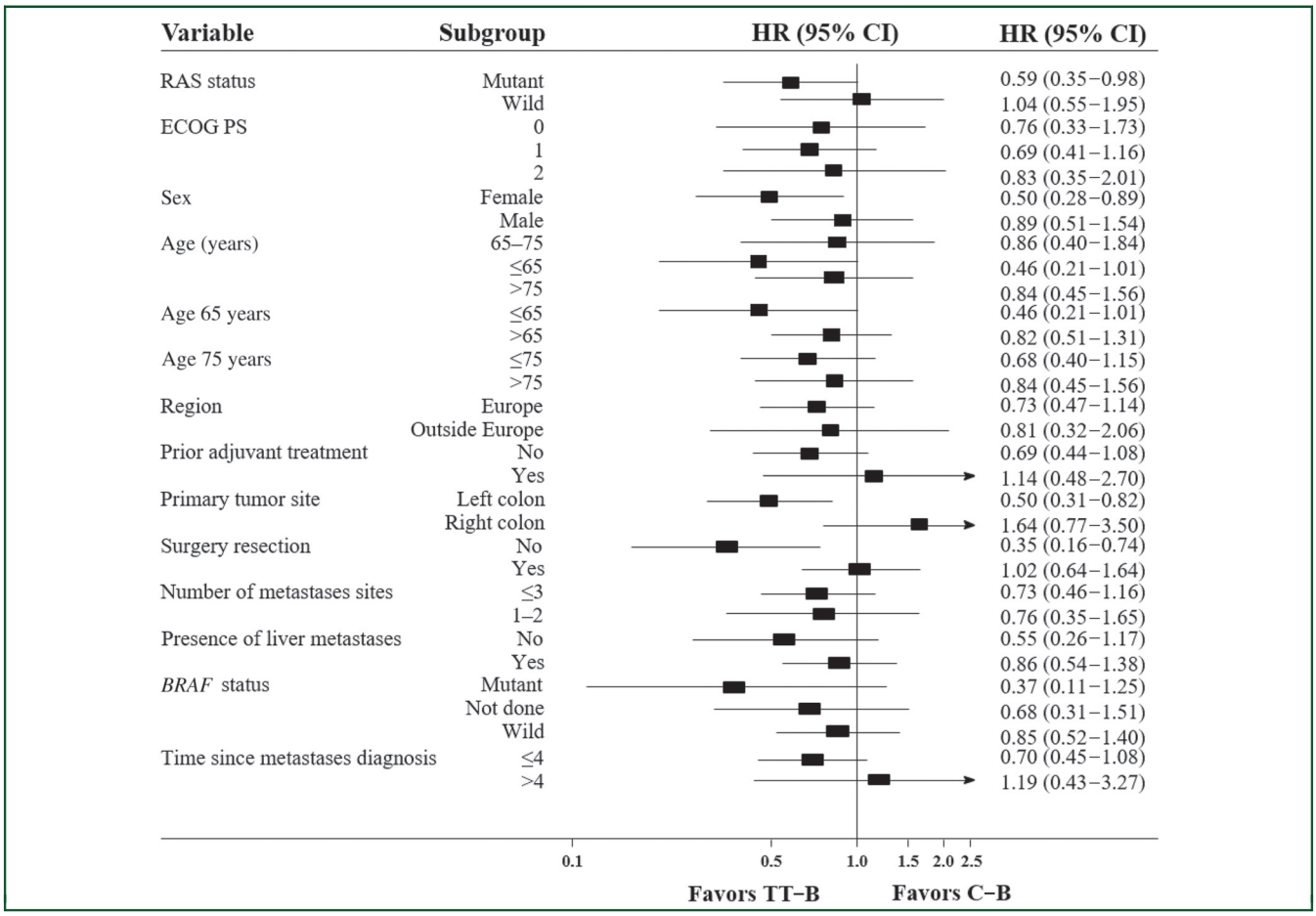

Figure 3. Forest plot for progression-free survival in subgroup analyses.
C—B, capecitabine plus bevacizumab; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; TT—B, trifluridine/tipiracil plus bevacizumab. The hazard ratio and its confidence interval are presented for information only.

Table 3. Frequency of adverse events in ≥10% of patients in each treatment group

	TT—B treatment ($N = 77$)		C—B treatment ($N = 76$)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Nonhematological events				
Diarrhea	41 (53)	1 (1)	33 (43)	6 (8)
Nausea	36 (47)	2 (3)	14 (18)	0 (0)
Decreased appetite	29 (38)	0 (0)	15 (20)	1 (1)
Fatigue	28 (36)	3 (4)	23 (30)	3 (4)
Vomiting	22 (29)	4 (5)	9 (12)	1 (1)
Malignant neoplasm progression	17 (22)	10 (13)	19 (25)	16 (21)
Alopecia	17 (22)	0 (0)	0 (0)	0 (0)
Asthenia	14 (18)	4 (5)	17 (22)	2 (3)
Stomatitis	13 (17)	1 (1)	16 (21)	0 (0)
Constipation	13 (17)	0 (0)	15 (20)	0 (0)
Hypertension	12 (16)	10 (13)	10 (13)	4 (5)
Abdominal pain	9 (12)	1 (1)	6 (8)	1 (1)
Weight decreased	9 (12)	1 (1)	6 (8)	0 (0)
Alanine aminotransferase increased	9 (12)	1 (1)	2 (3)	0 (0)
Viral upper respiratory tract infection	8 (10)	0 (0)	5 (7)	0 (0)
Dysgeusia	7 (9)	0 (0)	8 (11)	0 (0)
Dyspnea	6 (8)	0 (0)	8 (11)	1 (1)
Dizziness	5 (7)	0 (0)	8 (11)	0 (0)
Hand-foot syndrome	3 (4)	0 (0)	39 (51)	9 (12)
Hematological events				
Neutropenia	41 (53)	36 (47)	5 (7)	4 (5)
Anemia	24 (31)	8 (10)	5 (7)	0 (0)
Neutrophil count decreased	18 (23)	14 (18)	2 (3)	1 (1)
Febrile neutropenia	4 (5)	4 (5)	3 (4)	3 (4)
White blood cell count decreased	15 (20)	8 (10)	2 (3)	2 (3)
Thrombocytopenia	11 (14)	3 (4)	4 (5)	1 (1)
Blood bilirubin increased	6 (8)	1 (1)	9 (12)	2 (3)

Data are number (%) of patients as of 20 January 2018 (overall survival cutoff date). All treatment-emergent adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[14]
C—B, capecitabine plus bevacizumab; TT—B, trifluridine/tipiracil plus bevacizumab.

In conclusion, TT—B treatment showed promising clinical activity in first-line unresectable mCRC patients ineligible for intensive therapy, with an acceptable safety profile and no clinically relevant impact on the QoL. Further results can be expected from the ongoing comparative phase III study (SOLSTICE, NCT03869892) which is conducted in the same population setting as TASCO1.

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REFERENCES

1. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol*. 2016;27:1386—1422.
2. Peeters M, Cervantes A, Moreno Vera S, et al. Trifluridine/tipiracil: an emerging strategy for the management of gastrointestinal cancers. *Future Oncol*. 2018;14:1629—1645.
3. Lyseng-Williamson KA, Burness CB, Duggan ST. Trifluridine/tipiracil in metastatic colorectal cancer: a guide to its use. *Drugs Ther Perspect*. 2017;33:110—118.
4. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med*. 2015;372:1909—1919.
5. Yoshino T, Mizunuma N, Yamazaki K, et al. TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Oncol*. 2012;13:993—1001.
6. Van Cutsem E, Mayer RJ, Laurent S, et al. The subgroups of the phase III RECOURSE trial of trifluridine/tipiracil (TAS-102) versus placebo with best supportive care in patients with metastatic colorectal cancer. *Eur J Cancer*. 2018;90:63—72.
7. Van Cutsem E, Falcone A, Garcia-Carbonero R, et al. Proxies of quality of life in metastatic colorectal cancer: analyses in the RECOURSE trial. *ESMO Open*. 2017;2:e000261.
8. Cunningham D, Lang I, Marcuello E, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2013;14:1077—1085.
9. Price TJ, Zannino D, Wilson K, et al. Bevacizumab is equally effective and no more toxic in elderly patients with advanced colorectal cancer: a subgroup analysis from the AGITG MAX trial: an international randomised controlled trial of capecitabine, bevacizumab and mitomycin C. *Ann Oncol*. 2012;23:1531—1536.
10. Tebbutt NC, Wilson K, Gebski VJ, et al. Capecitabine, bevacizumab, and mitomycin in first-line treatment of metastatic colorectal cancer: results of the Australasian Gastrointestinal Trials Group Randomized Phase III MAX Study. *J Clin Oncol*. 2010;28:3191—3198.
11. Tsukihara H, Nakagawa F, Sakamoto K, et al. Efficacy of combination chemotherapy using a novel oral chemotherapeutic agent, TAS-102, together with bevacizumab, cetuximab, or panitumumab on human colorectal cancer xenografts. *Oncol Rep*. 2015;33:2135—2142.
12. Kuboki Y, Nishina T, Shinozaki E, et al. TAS-102 plus bevacizumab for patients with metastatic colorectal cancer refractory to standard therapies (C-TASK FORCE): an investigator-initiated, open-label, single-arm, multicentre, phase 1/2 study. *Lancet Oncol*. 2017;18:1172—1181.
13. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228—247.
14. National Cancer Institute. Common Terminology Criteria for Adverse Events. Version 4.0. NCI 2010. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Accessed June 28, 2019.
15. Cremolini C. When to use triplet chemotherapy as first-line treatment in metastatic colorectal cancer. *Clin Adv Hematol Oncol*. 2019;17:433—435.
16. Bossé D, Vickers M, Lemay F, Beaudoin A. Palliative chemotherapy for patients 70 years of age and older with metastatic colorectal cancer: a single-centre experience. *Curr Oncol*. 2015;22(5):e349—e356.
17. Falcone A, Ohtsu A, Van Cutsem E, et al. Integrated safety summary for trifluridine/tipiracil (TAS-102). *Anticancer Drugs*. 2018;29:89—96.
18. Yoshino T, Oki E, Nozawa H, et al. Rationale and design of the TRUSTY study: a randomised, multicentre, open-label phase II/III study of trifluridine/tipiracil plus bevacizumab versus irinotecan, fluoropyrimidine plus bevacizumab as second-line treatment in patients with metastatic colorectal cancer progressive during or following first-line oxaliplatin-based chemotherapy. *ESMO Open*. 2018;3:e000411.
19. Pfeiffer P, Yilmaz M, Möller S, et al. Trifluridine/tipiracil (TAS-102) with or without bevacizumab in patients with chemorefractory metastatic colorectal cancer. An investigator-initiated randomised study. *Lancet Oncol*. 2020;21:412—420.