Upfront FOLFOXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE2): a multicentre, open-label, phase 3, randomised controlled trial by GONO

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Summary

Background

The triplet FOLFOXIRI (fluorouracil, L-leucovorin, oxaliplatin, and irinotecan) plus bevacizumab showed improved outcomes of patients with metastatic colorectal cancer, when compared to FOLFIRI (fluorouracil, L-leucovorin, and irinotecan) plus bevacizumab. However, the actual benefit of the upfront exposure to the three cytotoxics when compared with a pre-planned sequential strategy of doublets was not clear, as well as the feasibility and efficacy of therapies after progression. To this purpose, we aimed at comparing a pre-planned strategy of upfront FOLFOXIRI followed by the reintroduction of the same regimen after disease progression to a sequence of mFOLFOX6 (fluorouracil, L-leucovorin, and oxaliplatin) and FOLFIRI doublets, in combination with bevacizumab.

Methods

TRIBE2 was an open-label, prospective, phase 3 randomised study of patients (aged 18–70 years with Eastern Cooperative Oncology Group [ECOG] performance status of 2 or less and aged 71–75 years with an ECOG performance status of 0), with unresectable, previously untreated metastatic colorectal cancer, who were recruited from 58 Italian Oncology Units. Patients were stratified according to center, ECOG performance status, primary tumour location and previous adjuvant chemotherapy,. A randomisation system incorporating a minimisation algorithm randomly assigned (1:1) patients via a masked web-based allocation procedure to two different strategies: first-line mFOLFOX6 (85 mg/m² of intravenous oxaliplatin concurrently with 200 mg/m² of L-leucovorin over 120 minutes; 400 mg/m² intravenous bolus of fluorouracil; 2400 mg/m² continuous infusion of fluorouracil for 48 hours) plus bevacizumab (5 mg/kg intravenously over 30 minutes) followed by FOLFIRI (180 mg/m² of intravenous irinotecan over 120 minutes concurrently with 200 mg/m² of L-

leucovorin; 400 mg/m² intravenous bolus of fluorouracil; 2400 mg/m² continuous infusion of fluorouracil for 48 hours) plus bevacizumab (5 mg/kg intravenously over 30 minutes) after disease progression (control group) or FOLFOXIRI (165 mg/m² of intravenous irinotecan over 60 minutes; 85 mg/m² intravenous oxaliplatin concurrently with 200 mg/m² of L-leucovorin over 120 minutes; 3200 mg/m² continuous infusion of fluorouracil for 48 hours) plus bevacizumab (5 mg/kg intravenously over 30 min) followed by the reintroduction of the same regimen after disease progression (experimental group). Combination treatments were administered up to 8 bi-weekly cycles followed by fluorouracil/L-leucovorin (same dose administered at the last induction cycle) plus bevacizumab maintenance until disease progression, unacceptable adverse events, or consent withdrawal. Both patients and investigators were aware of treatment assignment. The primary endpoint was progression-free survival 2, defined as the time from randomization to disease progression on any treatment given after first disease progression or death, analysed by intention to treat. Safety was assessed in the population of patients who received at least one dose of their assigned treatment. The study recruitment was completed, and follow-up of participants is still ongoing. The trial is registered at Clinicaltrials.gov: NCT02339116.

Findings

Between February 26, 2015, and May 15, 2017, 679 patients were randomly assigned and received treatment (340 in the control group and 339 in the experimental group). Most patients had ECOG Performance Status 0 (582 [86%] of 679), presented with synchronous metastases (604 [89%] of 679), and had a *RAS* (436 [64%] of 679) or *BRAF* mutated (66 [10%] of 679) tumour, while only a minority (109 [16%] of 679) had a left-sided and *RAS* and *BRAF* wild-type tumour. At data cut-off (July 30, 2019) the median follow-up was 35·9 months (IQR 30·1-41·4). Median progression-free survival 2 was 19·2 months (95% CI 17·3-21·4) in the

experimental group and 16·4 months (95% CI 15·1-17·5) in the control group (hazard ratio [HR] 0·74, 95% CI 0·63-0·88; p<0·001). During the first-line treatment, grade 3–4 adverse events were reported in 229 (68%) of 336 patients in the experimental group, and 155 (46%) of 336 in the control group (p<0·001). Higher incidences of all-cause grade 3-4 diarrhoea (57 [17%] of 336 vs 18 [5%] of 336, p<0·001), neutropenia (168 [50%] of 336 vs 71 [21%] of 336, p<0·001) and febrile neutropenia (22 [7%] of 336 vs 10 [3%] of 336, p=0·045) were reported in the experimental group. Serious adverse events occurred in 84 (25%) of 336 patients in the experimental group and in 56 (17%) of 336 patients in the control group. Eight treatment-related deaths were reported in the experimental group (two intestinal occlusions, two perforations, two sepsis, one myocardial infarction and one bleeding) and four in the control group (two occlusions, one perforation, one pulmonary embolism).

Interpretation

Upfront FOLFOXIRI plus bevacizumab followed by the reintroduction of the same regimen in case of disease progression is the best therapeutic strategy for patients with metastatic colorectal cancer selected according to the study criteria.

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Introduction

Several options are currently available for the upfront treatment of metastatic colorectal cancer patients. Based on the results of the phase III TRIBE study[1,2] and of other phase II randomized trials conducted worldwide,[3-6] the combination of the three-drugs regimen FOLFOXIRI (fluorouracil, L-leucovorin, oxaliplatin, and irinotecan) with the antiangiogenic bevacizumab is now regarded as a valuable first-line option by major guidelines.[7,8]

In fact, the previous TRIBE study by GONO demonstrated significantly better progression-free survival (hazard ratio [HR] for progression: 0·77 (95% CI: 0·65-0·93); p=0·003), primary endpoint of the study, response rate (odds ratio [OR] for response: 1·59 [95% CI: 1·10-2·28]; p=0·006) and overall survival (HR for death: 0·80 (95% CI: 0·65-0·98); p=0·030) with the triplet FOLFOXIRI plus bevacizumab when compared with the doublet FOLFIRI (fluorouracil, L-leucovorin, irinotecan) plus bevacizumab, at the price of an increased incidence of specific grade 3 and 4 adverse events (diarrhoea, stomatitis, neutropenia).[1,2]

However, since in the TRIBE study treatments after progression were left at investigators' choice and collected as post-study treatments, the efficacy of the triplet when compared with the exposure to the same agents in a sequential strategy of less toxic doublets was not demonstrated.[9] Furthermore, in spite of the significant benefit achieved in terms of overall survival with the intensified chemotherapy backbone, some concerns raised with regard to the feasibility and efficacy of treatments after progression following the upfront exposure to the three cytotoxics.

In the last years new recommendations were formulated based on results of clinical trials in the field of maintenance and treatments after progression: following a 4-6 months first-line treatment with a combination chemotherapy regimen plus bevacizumab, maintenance with a fluoropyrimidine plus bevacizumab until disease progression is recommended,[10-13] and the

continuation of angiogenesis inhibition also beyond disease progression is a valuable option supported by evidence from phase III trials.[14,15]

From these considerations, the TRIBE2 study was conceived in order to verify whether the upfront exposure to the three cytotoxics in the FOLFOXIRI regimen was superior to a pre-planned sequence of doublets (first-line mFOLFOX6 [fluorouracil, L-leucovorin, oxaliplatin], followed by FOLFIRI after disease progression), in the frame of a sustained inhibition of angiogenesis with bevacizumab in both groups. Upfront FOLFOXIRI plus bevacizumab is therefore compared with an oxaliplatin-based instead of an irinotecan-based doublet plus bevacizumab like in the previous TRIBE study.

Methods

Study design and participants

TRIBE2 (First-line FOLFOXIRI plus bevacizumab followed by reintroduction of FOLFOXIRI plus bevacizumab at progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab at progression in first- and second-line treatment of unresectable metastatic colorectal cancer) was a prospective, open-label, multicentre, randomized phase III study that included patients with metastatic colorectal cancer recruited from 58 Italian Oncology Units. Main inclusion criteria were the following: histologically confirmed colorectal adenocarcinoma; age between 18 and 75 years; Eastern Cooperative Oncology Group performance status 0–2 if age ≤70 years, or 0 if age 71–75 years; unresectable and measurable metastatic disease according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1;[16] adequate bone marrow, hepatic and renal function (neutrophils ≥1·5 × 10^9 cells per L, platelets ≥100 × 10^9 cells per L, and haemoglobin ≥90 g/L; serum bilirubin ≤1·5 times the upper limit of normal [ULN]; alanine aminotransferase and aspartate

aminotransferase ≤2·5 × ULN or ≤5 × ULN in the presence of liver metastases; alkaline phosphatase ≤2·5 × ULN or ≤5 × ULN in the presence of liver metastases; serum creatinine ≤1·5 × ULN or creatinine clearance >50 mL/min). Main exclusion criteria were previous palliative chemotherapy or biologic therapy for metastatic disease; adjuvant treatment with oxaliplatin; adjuvant treatment with fluoropyrimidine monotherapy completed less than 6 months before relapse; peripheral neuropathy of grade 2 or higher according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.[17]

The study was conducted in accordance with the Declaration of Helsinki and adhered to Good Clinical Practice guidelines. Approval for the protocol was obtained from local ethics committees of participating sites. All patients provided written informed consent to study procedures before enrolment. The study protocol is available at http://fondazionearco.org/studio-tribe-2/.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to receive either first-line mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab after disease progression (control group) or first-line FOLFOXIRI plus bevacizumab followed by reintroduction of FOLFOXIRI plus bevacizumab after disease progression (experimental group). All combination treatments were administrated up to 8 cycles followed by fluorouracil/L-leucovorin plus bevacizumab maintenance until disease progression, unacceptable adverse events, or consent withdrawal.

Eligible patients were randomized using a centralized web-based system with a minimization algorithm to obtain balanced assignment in each treatment group with respect to the stratification factors: centre, ECOG performance status (0 *versus* 1–2), primary tumour location (right-sided *versus* left-sided or rectum) and previous exposure to an adjuvant

treatment (yes *versus* no). The random allocation sequence was masked and was generated at the Clinical Trials Coordinating Center, Istituto Toscano Tumori (Florence, Italy). Treatment arm was not masked to both Investigators and participants.

Procedures

Patients received first-line induction with mFOLFOX6 plus bevacizumab (control group), consisting of an intravenous infusion of 5 mg/kg of bevacizumab over 30 min, followed by a 85 mg/m² intravenous infusion of oxaliplatin given concurrently with L-leucovorin at a dose of 200 mg/m² over 120 min, followed by a 400 mg/m² intravenous bolus of fluorouracil, and a 2400 mg/m² continuous infusion of fluorouracil for 48 hours, starting on day 1; or FOLFOXIRI plus bevacizumab (experimental group), consisting of an intravenous infusion of 5 mg/kg of bevacizumab over 30 min, followed by a 165 mg/m² intravenous infusion of irinotecan over 60 min, followed by an 85 mg/m² intravenous infusion of oxaliplatin given concurrently with L-leucovorin at a dose of 200 mg/m² for 120 min, followed by a 3200 mg/m² continuous infusion of fluorouracil for 48 h, starting on day 1. Treatment cycles were repeated every 14 days for up to 8 cycles.

The use of granulocyte colony-stimulating factor was not recommended as primary prophylaxis.

In the case of pre-specified adverse events, treatment modifications were allowed according to study protocol.

Thereafter, maintenance treatment with fluorouracil/L-leucovorin and bevacizumab was planned in both groups at same dose used at the last cycle of the induction treatment, every 14 days, until progressive disease, patient's refusal, unacceptable adverse events or consent withdrawal.

At the first evidence of disease progression, both during induction or maintenance, patients enrolled in the control group received FOLFIRI plus bevacizumab (5 mg/kg intravenous infusion of bevacizumab for 30 minutes, followed by 180 mg/m² intravenous infusion of irinotecan for 120 min given concomitantly with a 200 mg/m² intravenous infusion of L-leucovorin, followed by a 400 mg/m² intravenous bolus of fluorouracil, and a 2400 mg/m² continuous infusion of fluorouracil for 48 hours, starting on day 1), repeated every 14 days for a maximum of 8 cycles, then followed by fluorouracil/L-leucovorin and bevacizumab maintenance. In the case of disease progression during maintenance, patients enrolled in the experimental group received the re-induction of FOLFOXIRI plus bevacizumab (according to the above described schedule) up to 8 cycles, followed by fluorouracil/L-leucovorin and bevacizumab as maintenance. If disease progression occurred during the first-line induction with FOLFOXIRI plus bevacizumab, a second-line treatment at investigator' s choice was allowed.

In the case of surgical radical resection of residual metastases, post-operative therapy with the same pre-operative regimen was planned up to an overall duration of 6 months (12 cycles), then followed by fluorouracil/L-leucovorin with bevacizumab up to 6 months after resection.

The assessment of response and progression was based on investigator-reported measurements, subsequently confirmed by a central review, and was performed according to RECIST 1.1 criteria with CT scans repeated every 8 weeks. [16] The multidisciplinary discussion of resectability by an experienced and dedicated local team was planned at the time of every disease re-assessment.

At the start of every cycle, the patients' medical history, ECOG performance status, results of physical examination, and adverse events were recorded and graded according to the NCI-CTCAE version 4.0.[17]

Outcomes

To properly assess the efficacy of the whole first- and second-line strategy, the primary endpoint was progression-free survival 2, defined as the time from randomization to disease progression, according to RECIST version 1.1,[16] on any treatment given after first disease progression, or death from any cause. For patients who did not receive any treatment within 3 months after first disease progression, progression-free survival 2 was equal to 1st progression-free survival, defined as the time from randomization to the first evidence of disease progression, or death from any cause. Secondary endpoints included 1st progression-free survival, 2nd progression-free survival, defined as the time between the first and the second evidence of disease progression or death from any cause, safety, the proportion of patients achieving response, the proportion of patients achieving early objective response, the proportion of patients undergoing R0 resection of metastases (*i.e.*, no macroscopic or microscopic residual tumour), time to failure of strategy, and overall survival. The analysis of early objective responses will be based on the central assessment of CT scans that was not performed yet. Data of treatments received after the second disease progression are needed to calculate the time to failure of strategy and are not yet mature.

Statistical analysis

To detect a hazard ratio (HR) for progression-free survival 2 of 0·77 (corresponding to an increase in the progression-free survival 2 rate at 15 months from 50% to 60%) in favour of

the experimental group with an overall two-sided alpha error of 5% and an estimated power of 80%, we planned to enrol 654 patients in order to observe 466 events of progression-free survival 2 or death from any cause.

An interim analysis was planned to assess the superiority of the experimental group versus the control group for the primary endpoint when 2/3 of the expected progression-free survival 2 events had occurred (303 out of 466 events). According to the O'Brien Fleming spending rule, two-sided alpha levels of significance were set at 0·0131 and 0·0455 for the interim and final analysis, respectively. At the data cut-off of 30th July 2018, 423 PFS2 events were collected and the interim analysis was conducted (figure S1, appendix).

All efficacy analyses were performed on an intention-to-treat basis. Safety, including summary of adverse events, was assessed in all enrolled patients who received at least one dose of study treatment (safety population). 2nd progression-free survival was assessed also in the per protocol population, including patients that received the treatment after progression planned according to the random assignment. The rate of adverse events was evaluated in the safety population, including patients who received at least one cycle of the study treatment. The median period of follow-up was calculated for the entire study cohort according to the reverse Kaplan-Meier method. Distributions of time-to-event variables for progression-free survival 2, 1st and 2nd progression-free survival, and overall survival were estimated with the use of the Kaplan-Meier product-limit method. The log-rank test was used as primary analysis for treatment groups' comparison. Cox proportional-hazards modelling was also performed as supportive analyses. *Post-hoc* exploratory subgroup analyses of progression-free survival 2, 1st progression-free survival and overall survival were performed by means of an interaction test to determine the consistency of the treatment effect according to key baseline characteristics. The proportion of patients achieving response, R0 resection of metastases, and reporting

adverse events in the two groups were compared with the use of the chi-square test for heterogeneity or with Fisher's exact test when appropriate; odds ratios and 95% confidence intervals were estimated with a logistic-regression model. All statistical tests were two-sided, and p values of 0·05 or less were deemed significant. No adjustments for multiple comparisons were performed.

Statistical analyses were done using SAS version 9.2.

Data about *RAS* (codons 12, 13, 59, 61, 117 and 146 of *KRAS* and *NRAS*) and *BRAF* (V600E mutation) mutational status were collected at baseline based on the local assessment performed on the primary tumour and/or related metastases. Microsatellite instability was centrally analysed *post-hoc* by means of immunohistochemistry on primary tumour and/or related metastases, as previously reported.[18-20] For all molecular analyses, tumour specimens were archival tissues collected before study treatment.

The trial is registered with ClinicalTrials.gov, number NCT02339116.

Role of the funding source

The Italian GONO Foundation sponsored the trial and GONO investigators were responsible for study design, data collection, data analysis, and data interpretation. The writing of the report and the decision to submit for publication was the responsibility of the GONO Foundation. The no-profit ARCO Foundation supported molecular analyses, but had no role in study design, data collection, data analysis, data interpretation, or writing of the report. F. Hoffman-La Roche partially supported the trial with a research grant and providing bevacizumab for the whole study treatment of the experimental group and for the treatment beyond progression of the control group, but had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full

access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From February 26th, 2015 to May 15th, 2017, 679 patients with metastatic colorectal cancer were randomly assigned to the control (n=340) or the experimental group (n=339) (figure 1) and were included in the intention-to-treat population. Six hundred and seventy-two patients (336 per group) received at least one dose of study treatment and were included in the safety population. One patient per arm was never treated; two patients in the control group and three in the experimental group received other treatments. One patient allocated to the control group received the experimental treatment and was included in the experimental group for safety analyses. The cut-off date for the present analysis was July 30th, 2019.

Patients' demographic, clinical and molecular baseline characteristics were well balanced in the two groups (table 1). The median (interquartile range [IQR]) age of the study population was 61 (53-67) years. Five hundred and eighty-two (86%) of 679 patients had an ECOG Performance Status of 0; 259 (38%) had a right-sided primary tumour, 399 (59%) had multiple sites of metastases and 201 (30%) had liver-limited disease. *RAS* and *BRAF* mutations were found in 436 (64%) and 66 (10%) cases, respectively, and 26 (5%) patients had microsatellite instable (MSI-high) tumours. Only 109 (16%) of 679 patients (53 [16%] of 340 and 56 [17%] of 339 in the control and in the experimental group, respectively) had left-sided and *RAS* and *BRAF* wild-type tumours.

At a median follow-up of 35·9 months (IQR 30·1-41·4), 546 (80%) of 679 events of progression-free survival 2 (286 [84%] of 340 in the control group and 260 [77%] of 339 in the experimental group) were observed. Median progression-free survival 2 was 19·2 months

(95% CI 17·3–21·4) in the experimental group and 16·4 months (95% CI 15·1–17·5) in the control group (HR 0·74, 95% CI 0·63–0·88; log-rank test p<0·001; figure 2A). Treatment effect was consistent across all analysed clinical and molecular subgroups (figure S2, appendix). When combining primary tumour sidedness and *RAS* and *BRAF* mutational status, a heterogeneous effect of treatment intensification across subgroups was evidenced (p for interaction=0·043).

First-line disease progression occurred in 605 (89%) of 679 patients: 310 (91%) of 340 in the control group and 295 (87%) of 339 in the experimental group. Median 1st progression-free survival was 12·0 months (95% CI 11·1-12·9) in the experimental group receiving FOLFOXIRI plus bevacizumab, and 9·8 months (95% CI 9·0-10·5) in the control group receiving mFOLFOX6 plus bevacizumab (HR 0·74, 95% CI 0·63-0·86; log-rank test p<0·001; figure 2B). Treatment effect was consistent across all analysed clinical and molecular subgroups (figure S3). The proportion of patients achieving response according to RECIST 1.1 was 62% (210 of 339) in the experimental group as compared with 50% (171 of 340) in the control group (odds ratio 1·61, 95% CI 1·19–2·18; p=0·002). The proportion of patients undergoing R0 resection of metastases was 17% (58 of 339) in the experimental group and 12% (41 of 340) in the control group (odds ratio 1·55, 95% CI 1·00-2·39; p=0·047).

The incidence of grade 3 or 4 neutropenia, febrile neutropenia and diarrhoea was significantly higher in the experimental than in the control group (table 2). Serious adverse events occurred in 84 (25%) of 336 patients in the experimental group and in 56 (17%) of 336 patients in the control group. Twenty-two (7%) of 339 and 13 (4%) of 340 patients died within 6 months from randomisation in the experimental and in the control group, respectively. Eight deaths in the experimental group were due to fatal adverse events: two intestinal occlusions, two intestinal perforations, two sepsis, one myocardial infarction and one bleeding. Four

deaths in the control group were due to fatal adverse events: two occlusions, one perforation, and one pulmonary embolism. Fourteen and nine deaths within 6 months from randomisation were due to rapid disease progression in the experimental and in the control group, respectively. Data about treatment exposure were detailed in table S1 (appendix). One-hundred and ninety-five (58%) of 336 patients in the experimental group and 159 (47%) of 336 patients in the control group required dose reduction. Eleven (3%) of 336 patients per group discontinued the treatment for drug-related toxicity.

Out of 570 patients still alive at the time of first disease progression, 259 (88%) of 296 in the control group and 224 (82%) of 274 in the experimental group received a further treatment (figure 1; table S2, appendix). The 2nd progression-free survival analysis was based on 511 (90%) of 570 events – 272 (92%) of 296 in the control group and 239 (87%) of 274 in the experimental group. Median 2nd progression-free survival was 6·2 months (95% CI 5·6-6·6) in the experimental group and 5·6 months (95% CI 4·9–6·4) in the control group (HR 0·87, 95% CI 0·73–1·04; log-rank test p=0·114; figureS4A).

Two-hundred and one (78%) of 259 patients in the control group and 132 (59%) of 224 in the experimental group received the treatment after progression planned according to the random assignment (FOLFIRI plus bevacizumab and FOLFOXIRI plus bevacizumab, respectively) and were included in the per protocol population (figure 1; table S2, appendix).

In the per protocol population, the 2nd progression-free survival was based on 186 (93%) of 201 events in the control group and 115 (87%) of 132 in the experimental group. Median 2nd progression-free survival was 6·5 months (95% CI 6·2–7·5) in the experimental group and 5·8 months (95% CI 4·9–6·5) in the control group (HR 0·79, 95% CI 0·63–1·00; log-rank test p=0·048; figure S4B).

No significant differences in the incidence of grade 3 or 4 adverse events between FOLFIRI plus bevacizumab and FOLFOXIRI plus bevacizumab, given after disease progression, were observed, with the only exception of neurotoxicity, whose incidence was significantly higher in the experimental (6 [5%] of 132) than in the control group (0 of 201) (table 2). Serious adverse events occurred in 20 (15%) of 132 patients in the experimental group and 25 (12%) of 201 patients in the control group. Three treatment-related deaths were reported in the experimental group (two intestinal occlusions and one sepsis) and four in the control group (one intestinal occlusion, one intestinal perforation, one cerebrovascular event and one sepsis). Six (5%) of 132 patients in the experimental group and 1 (0·5%) of 201 patients in the control group discontinued the treatment for drug-related toxicity. Data about treatment exposure were detailed in table S1 (appendix).

The overall survival analysis was based on 459 (68%) of 679 events – 241 (71%) of 340 in the control group and 218 (64%) of 339 in the experimental group. Most deaths were due to disease progression (226 [94%] of 241 in the control group and 199 [91%] of 218 in the experimental group). Eight (3%) of 241 and 11 (5%) of 218 deaths in the control and in the experimental group were due to treatment-related adverse events. Seven (3%) of 241 and eight (3%) of 218 were related to other reasons. Median overall survival was 27·4 months (95% CI 23·7-30·0) in the experimental group and 22·5 months (95% CI 20·7-24·8) in the control group (HR 0·82, 95% CI 0·68-0·98; log-rank test p=0·032; figure 3). Treatment effect was consistent across all analysed clinical and molecular subgroups (figure S5, appendix). A significant interaction effect between treatment and ECOG Performance Status was reported (p for interaction=0·021).

Discussion

Our findings demonstrate the superiority of the upfront exposure to FOLFOXIRI plus bevacizumab followed by the re-induction with the same agents when compared with a pre-planned sequential strategy of administration of the three cytotoxics across two subsequent lines of therapy (mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab after disease progression) in the treatment of patients with metastatic colorectal cancer. Of note, the percentage of patients enrolled in the control group and actually exposed to the three cytotoxics was as high as 88%, thus further strengthening the clinical significance of the advantage reported by the experimental group.

We provide a meaningful demonstration of the efficacy of FOLFOXIRI plus bevacizumab administered up to 8 cycles as first-line option for metastatic colorectal cancer patients, by corroborating results previously achieved in the TRIBE trial, where the treatment was planned up to 12 cycles.[1,2] Indeed, FOLFOXIRI plus bevacizumab was associated with statistically significant and clinically relevant improvements in the proportion of patients achieving response, in progression-free and overall survival in a population with initial poor prognostic features, thus showing the impact of the first-line regimen on the therapeutic route of patients with metastatic colorectal cancer, and particularly the high magnitude of the effect of the upfront intensified treatment on patients' long-term outcome. In fact, the 89% of patients included in the TRIBE2 study presented with synchronous metastases, the 38% had a right-sided primary tumour, the 59% had more than one metastatic site, and the 64% and 10% bore a *RAS* or *BRAF* mutated tumour, respectively. These poor prognostic features may explain the shorter duration of overall survival reported in both groups, when compared with results in the *RAS* wild-type population of other recent randomised trials.[21-25] Differently from TRIBE, an initial cross of overall survival curves is observed, probably due to the numerically higher occurrence of early deaths (within six months from randomisation) in the experimental group

as a consequence of both fatal adverse events and rapid disease progressions. However, these differences were not statistically significant.

In terms of safety, the toxicity profiles of study regimens were consistent with the known adverse events of the individual drugs, and highly coherent with results from previous studies investigating the triplet plus bevacizumab.[1,3-6,26-30] The TRIBE2 study was conducted in 58 Italian sites, highlighting the large scale feasibility of the experimental strategy.

We also showed that treatments after progression to first-line FOLFOXIRI plus bevacizumab, then followed by maintenance with fluorouracil/L-leucovorin plus bevacizumab, were feasible in the 82% of patients, and their efficacy was not affected by the upfront exposure to the three cytotoxics, as demonstrated by the absence of difference in terms of 2nd progression-free survival between the two study groups. FOLFOXIRI plus bevacizumab was reintroduced after disease progression in the 59% of patients in the experimental group, and a per protocol analysis reported a significant advantage in terms of 2nd progression-free survival in these patients when compared with those who received FOLFIRI plus bevacizumab after progression to first-line mFOLFOX6 plus bevacizumab, with no increase in grade 3 or 4 adverse events except for an expected higher incidence of neuropathy. The relatively good tolerability is probably explained by a careful clinical selection of those patients able to receive FOLFOXIRI plus bevacizumab after progression, made by treating physicians on the basis of their previous tolerance to this regimen and of the health status of patients.

With regard to treatments after progression, a potential limitation of our study is the choice to switch to FOLFIRI after first-line mFOLFOX6 instead of re-introducing an oxaliplatin-based regimen. Even if this strategy was previously evaluated in clinical trials,[31,32] our choice was driven by the objective of exposing the highest percentage of patients to the three cytotoxics

also in the control group. Moreover, by a pragmatic point of view, the switch to the alternate doublet is the most common approach in the daily clinical practice.

As shown by the subgroup analyses, no interaction was observed between treatment effect and *RAS* and *BRAF* mutational status, as in the previous TRIBE study. Nonetheless, based on the high magnitude of benefit reported in the small subgroup of patients with *BRAF* mutated tumours in the previous TRIBE,[1,2] FOLFOXIRI plus bevacizumab was identified as a preferable option in this subgroup. The evidence of no increased benefit from the intensified approach reported here may be explained by the different comparator group (oxaliplatin- instead of irinotecan-based doublet) and/or the molecular and clinical heterogeneity of *BRAF* mutated tumours. In particular, though recognizing the exploratory nature of analyses focusing on very small subgroups, among *BRAF* mutated patients a different effect of treatment intensification according to primary tumour sidedness was suggested consistently with previous findings of the TRIBE study.[33]

In order to properly translate our study in the current landscape of the first-line treatment of metastatic colorectal cancer, it should be acknowledged that the 86% of enrolled patients had an ECOG Performance Status of 0, the median age of the study population was relatively young (61 years), and only a minority (16%) of them had a left-sided and *RAS* and *BRAF* wild-type tumour. This might be explained by the increased use of chemotherapy plus an anti-Epidermal Growth Factor Receptor (EGFR) monoclonal antibody as first-line treatment of patients with *RAS* and *BRAF* wild-type tumours during the accrual of the TRIBE2 study. Moreover, it should be pointed out that at the time of TRIBE2 conception and during most of the recruitment period, sidedness was not relevant as a driver for therapeutic choices in first line, yet. As a consequence, the optimal candidates to first-line doublets plus anti-EGFR are under-represented in the present study and the combination of an anti-EGFR with

chemotherapy remains a preferred option for these patients. To date, the role of the triplet plus an anti-EGFR monoclonal antibody as first-line treatment has been investigated in phase II trials[34,35] and a phase III trial to assess the added value of the intensification of the chemotherapy backbone is currently ongoing.[36] On the other side, a relevant magnitude of benefit was reported among patients with a right-sided and/or a *RAS* mutated tumour, thus making upfront FOLFOXIRI plus bevacizumab the best first-line option for patients in this subgroup as evidenced to date.

Contributors

CCr, CA, DR, SL, FL, FP, RB, TPL, ET, DS, AP, FM, RG, GA, AZ, SMu, CG, AB, RM, SC, SCo, LA, GT, GM, MR, SDD, CCa, MC, GR, AM, MR, SCu, SMa, EF, EC, VZ and AF collected data and recruited patients. CCr, CA, DR, LB, and AF analysed and interpreted the data. CCr, CA, DR, FM, RM, GM, LB and AF wrote the manuscript. CCr, LB, FL and AF designed the study. CU and GF performed molecular analyses. All authors revised and approved the manuscript.

Declarations of interest

CCr received personal fees from Roche, Amgen, Bayer, Servier, research funding from Merck Serono, and has a consulting or advisory role with Roche, Bayer, Amgen. DR received personal fees from Takeda.

SL received personal fees from Roche, Lilly, Bristol-Myers Squibb, Servier, Merck Serono, research funding from Amgen, Merck Serono, and has a consulting or advisory role with Amgen, Merck Serono, Lilly, Servier. FL received personal fees from Roche, Sanofi, Bayer, Amgen, research funding from Roche, Merck Serono, Amgen, Bayer, and has a consulting or advisory role with Amgen, Sanofi, Bayer, Amal. FP received personal fees from Amgen, Merck Serono, Roche, Sanofi, Bayer, Servier, Lilly, research funding from Bristol-Myers Squibb, and has a consulting or advisory role with Amgen, Merck Serono, Bayer, Lilly, Sanofi, Roche, Servier. RB received personal fees from and has a consulting or advisory role with Bayer, AstraZeneca, Sanofi, Novartis, Amgen, Roche, Pfizer, Jansen, Bristol-Myers Squibb. GA received personal fees from and has consulting or advisory role with Merck Serono, Amgen, Roche, Servier. AZ received personal fees from and has consulting or advisory role with Amgen, Bayer, Lilly, Merck Serono, Servier, Sanofi. SCo received personal fees from Roche, Sanofi, Servier, Merck Serono, Lilly, research funding from Roche, Merck Serono, Amgen, Servier, Lilly, has a consulting or advisory role with Amgen, Sanofi, Bayer, Servier, Merck Serono, Ipsen. VZ received personal fees from Bayer, Roche, Bristol-Myers Squibb, Astellas Pharma, Servier, AstraZeneca, Lilly,

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Data sharing

Qualified researchers may request to GONO Foundation access to individual patient-level data. Data will be provided with an accompanying dictionary defining each field in the set and clinical study documentation. The study protocol is available online at http://fondazionearco.org/studio-tribe-2/. Further details on GONO Foundation global policy on sharing of clinical information will be available by emailing to info@gonogroup.org or to the corresponding author.

Panel: Research in context

Evidence before study

A previous phase 3 trial (TRIBE study) by the Italian GONO Foundation proved the superiority of the first-line triplet regimen FOLFOXIRI (fluorouracil, L-leucovorin, oxaliplatin, and irinotecan) over the doublet FOLFIRI (fluorouracil, L-leucovorin, and irinotecan) when bevacizumab was added to both regimens in patients with unresectable metastatic colorectal cancer. Based on these results, FOLFOXIRI plus bevacizumab is supported by all major clinical guidelines as a valuable first-line option for metastatic colorectal cancer patients, selected according to the pivotal TRIBE study criteria. However, some concerns raised about the use of FOLFOXIRI in the daily practice, including the actual benefit of the exposure to all the three cytotoxics as compared with the pre-planned sequential administration of the same drugs in oxaliplatin- and irinotecan-based doublets, and the feasibility and the efficacy of treatments after progression.

We searched Pubmed since database inception until July 30th, 2019, for the terms "FOLFOXIRI", "triplet", "doublets", "FOLFOX", "XELOX", "FOLFIRI", "XELIRI", "bevacizumab", "reintroduction", "second-line", "strategy trial". Only publications in English were considered. We found only a few reports that retrospectively described a favourable outcome of second-line therapies, including the reintroduction of the triplet, given after failure of first-line FOLFOXIRI in non-randomly assigned subgroups, and no trials that prospectively compared the efficacy of the upfront use of FOLFOXIRI versus a standard sequential strategy of oxaliplatin- and irinotecan-based doublets.

Herein, we report results of the phase III TRIBE2 study, designed with the purpose to investigate whether the upfront use of FOLFOXIRI improves the clinical outcome of unresectable metastatic colorectal cancer patients, when compared with the pre-planned,

sequential use of mFOLFOX6 and FOLFIRI. In both strategies bevacizumab is added upfront and after progression, to exploit the effectiveness of a prolonged inhibition of angiogenesis, alternating short (up to 4 months) induction periods and less intensive maintenance phases.

Added value of this study

Current data provide additional evidence of the impact of the upfront use of FOLFOXIRI plus bevacizumab on the survival of unresectable metastatic colorectal cancer patients, demonstrating its superiority when compared with a sequential strategy of doublets plus bevacizumab. The efficacy of treatments after progression to FOLFOXIRI plus bevacizumab is clearly shown, and the beneficial effect of the reintroduction of the triplet in selected patients is suggested for the first time.

Implications of all the available evidence

Based on these results upfront FOLFOXIRI plus bevacizumab followed by the reintroduction of the same regimen in case of disease progression is the best therapeutic option for metastatic colorectal cancer patients who meet the study inclusion criteria.

Tables and Figures

Table 1. Baseline characteristics of patients in the intention to treat population.

Table 2. All-cause adverse events, occurring during first-line therapy in the safety population and during therapy administered after disease progression in the per protocol population, according to treatment group.

Figure 1. TRIBE2 study consort diagram.

§ One patient allocated to control group received the experimental study treatment and was included in the experimental group in the safety population; *two patients in the control group and three patients in the experimental group died the same day of disease progression and were not included in the population for the analysis of 2nd progression-free survival. Control group indicates mFOLFOX6 plus bevacizumab, followed after disease progression by FOLFIRI plus bevacizumab. Experimental group indicates FOLFOXIRI plus bevacizumab, followed after disease progression by FOLFOXIRI plus bevacizumab. FOLFIRI: fluorouracil, L-leucovorin, and irinotecan; FOLFOXIRI: fluorouracil, L-leucovorin, oxaliplatin and irinotecan; FOLFOX: fluorouracil, L-leucovorin, and oxaliplatin; bev: bevacizumab; PD, progressive disease.

Figure 2. Progression-free survival 2 and first progression-free survival.

A.

B.

Kaplan Meier estimates of progression-free survival 2 in the intention to treat population (A) and Kaplan Meier estimates of 1st progression-free survival in the intention to treat population (B), according to treatment group.

CI, confidence interval; HR, hazard ratio; mos, months; pts, patients. Panel A. Control group indicates mFOLFOX6 plus bevacizumab, followed after disease progression by FOLFIRI plus bevacizumab. Experimental group indicates FOLFOXIRI plus bevacizumab, followed after disease progression by FOLFOXIRI plus bevacizumab. Panel B. Control group indicates first-line induction with mFOLFOX6 plus bevacizumab, followed by maintenance with fluorouracil/L-leucovorin plus bevacizumab. Experimental group indicates first-line induction with FOLFOXIRI plus bevacizumab, followed by maintenance with fluorouracil/L-leucovorin plus bevacizumab.

Figure 3. Overall survival.

Kaplan Meier estimates of overall survival in the intention to treat population, according to treatment group.

CI, confidence interval; HR, hazard ratio; mos, months; pts, patients. Control group indicates mFOLFOX6 plus bevacizumab, followed after disease progression by FOLFIRI plus bevacizumab. Experimental group indicates FOLFOXIRI plus bevacizumab, followed after disease progression by FOLFOXIRI plus bevacizumab.

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