Effectiveness of bevacizumab added to standard chemotherapy in metastatic colorectal cancer: final results for first-line treatment from the ITACA randomized clinical trial

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Background: We report the results from a first-line phase III randomized clinical trial on metastatic colorectal cancer (mCRC) aimed at evaluating the effectiveness of adding bevacizumab (B) to standard first-line chemotherapy (CT).

Patients and methods: mCRC patients were randomized to receive first-line CT (FOLFIRI or FOLFOX4) plus B (arm A) or CT only (arm B). The primary end point was progression-free survival (PFS). Secondary end points included overall survival (OS), response rate (ORR) and safety. Three hundred and fifty patients and 310 events were required to have an 80% statistical power to detect a difference in PFS between the groups.

Results: Between November 2007 and March 2012, 376 patients were randomized. About 60% of patients received FOLFOX4 and 40% FOLFIRI. After a median follow-up of 36 months, 343 progressions and 275 deaths had been observed in the overall population. The median PFS was 9.6 [95% confidence interval (CI) 8.2–10.3] and 8.4 (95% CI 7.2–9.0) months for arms A and B, respectively, with a hazard ratio of 0.86 (95% CI 0.70–1.07; \( P = 0.182 \)). No statistically significant differences in OS or ORR were observed. B-containing regimens were associated with more frequent hypertension, bleeding, proteinuria and asthenia.

Conclusions: The addition of B to standard first-line CT for mCRC did not provide a benefit in terms of PFS, OS or ORR. Further research is warranted to better identify the target population.

Clinical trial number: NCT01878422.

Key words: metastatic colorectal cancer, chemotherapy, bevacizumab, randomized clinical trial

introduction

Colorectal cancer (CRC) is the third most common form of cancer and the second leading cause of cancer-related deaths in Western countries [1]. The median overall survival (OS) for metastatic disease, without specific treatments, is 6 months or less [2].

For several decades, 5-fluorouracil (5-FU) was the only approved drug to treat CRC, producing minimal benefits over support therapy [3]. In the 1990s, the introduction of irinotecan and oxaliplatin into a 5-FU-based regimen led to a significant increase in response rates and OS which, in several studies, was more than 20 months [3–5]. Bevacizumab (B), a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor, has been found to improve survival in both first- and second-line settings when added to chemotherapy (CT). Although first-line randomized clinical trials (RCTs) have clearly demonstrated the efficacy of B in combination with the IFL (irinotecan, bolus 5-FU, leucovorin) regimen [6] and with fluoropyrimidines [7–9], they have produced less convincing or negative results when B is combined with standard combination regimens [10, 11]. Furthermore, to date, few studies have been designed to identify the best sequence for the first- and second-line treatment of metastatic CRC (mCRC).

We designed an academic, multicenter, open-label randomized trial to define the role of targeted therapy in combination...
with CT in the management of patients with mCRC [Italian Trial in Advanced Colorectal Cancer (ITACA)] (supplementary Figure S1, available at Annals of Oncology online). This report presents the results from the first-line randomized phase III study, designed to determine the effect of adding B to standard CT on progression-free survival (PFS).

patients and methods

patients

Patients aged ≥18 years with histologically confirmed mCRC, one or more unidimensionally measurable lesions not amenable to curative resection, an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 (≤1 if aged ≥70 years) and an estimated life expectancy of at least 12 weeks, were enrolled on to the trial. Previous adjuvant chemotherapy for CRC or neo-adjuvant/adjuvant chemo-radiotherapy for rectal cancer were permitted if completed at least 6 months before recurrence; prior treatments with any anti-EGFR or anti-angiogenesis agents as well as prior chemotherapy or immunotherapy for metastatic or advanced disease were not allowed.

Patients were required to have adequate hematologic, hepatic and renal functions and D-dimer within normal range (if abnormal, thromboembolic events had to be excluded). Exclusion criteria were as follows: pregnant or breast-feeding women; clinically significant cardiovascular disease; uncontrolled hypertension; bleeding diathesis or coagulopathy; pulmonary embolism or any arterial thromboembolism, deep vein thrombosis or other significant thromboembolic events, clinically significant peripheral vascular disease; chronic use of aspirin (>325 mg/day) anti-platelet agents or anticoagulants; proteinuria (if protein >30 mg/dl or +1, ≤1 g of protein/24 h required); known central nervous system metastases.

The study was carried out in accordance with the principles of Good Clinical Practice and the ethical standards laid down in the Declaration of Helsinki. The protocol was approved by the local Ethical Committee for each study site and written informed consent was obtained from each patient.

treatment

All eligible patients were randomized to either CT plus B (arm A) or CT alone (arm B). CT was FOLFIRI or FOLFOX4, at the discretion of the clinician, for both arms. The FOLFIRI and FOLFOX4 regimens were as previously described [12, 13]. B was administered as a 30–90 min intravenous infusion at a dose of 5 mg/kg on day 1 of each 2-week cycle. Treatment was to be continued until disease progression (PD), withdrawal of consent or unacceptable toxicity, whichever came first. Pre-specified dose modifications of CT were provided after the occurrence and resolution of severe hematologic or non-hematologic toxicity.

If a patient became eligible for curative resection of metastatic disease, B was to be stopped at least 6–8 weeks before the planned date of surgery. After surgery, the choice of treatment was at the discretion of the treating physician and patients could restart treatment with CT (and/or B in arm A) at least 28 days after surgery or complete wound healing, until progressive disease (PD). Upon progression, all eligible patients could be randomized on to one of two independent (ongoing) second-line trials (supplementary Figure S1, available at Annals of Oncology online):

- Study 153 01/2A: Arm A patients with wild-type KRAS are randomized to the other CT regimen (FOLFIRI or FOLFOX) or the other CT plus cetuximab. Arm A patients with mutated KRAS are not randomized and are treated with the other CT regimen alone.
- Study 153 01/2B: Arm B patients with wild-type KRAS are randomized to the other CT plus B or the other CT plus B plus cetuximab. Given that the detrimental effect of the combination of two monoclonal antibodies observed in the CAIRO2 and PACCE phase III trials appeared to be limited to KRAS-mutated patients, it was unanimously decided to maintain this arm active and closely monitor safety profiles [14, 15]. Arm B patients with mutated KRAS are not randomized and are treated with the other CT plus B.

All patients were followed until death, and data on the second-line treatments administered were recorded.

Response Evaluation Criteria in Solid Tumors (RECIST) guidelines were used to define all responses. An independent central review of patient scans was not carried out. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) for Adverse Events, Version 3. Pre-defined adverse events of special interest for B were proteinuria, hypertension, wound healing complications, thromboembolic events, gastrointestinal perforation, abscess or fistula and bleeding.

trial design

The primary aim of the original protocol was OS, but this was amended as a result of poor recruitment (amendment 2, 9 March 2011), changing the primary objective to PFS. Secondary efficacy end points were OS, overall response rate (ORR) and the safety profile of the administered treatments. Patients were randomized in a 1:1 allocation ratio. Separate randomization lists using a permuted block balanced procedure were generated for each participating center, stratified by the CT regimen and by KRAS status (wild-type/unknown or mutated, according to amendment no. 1, 3 May 2009).

statistical methods and considerations

PFS was defined as the time from random assignment to the first documentation of PD (per investigator assessment), or death from any cause. Patients undergoing curative metastasectomy were censored at the time of surgery.

As a function of the second amendment, the study was planned to have more than 80% power at the 5% significance level (two-sided) to detect a 27% relative reduction in the progression rate (absolute increase in PFS of 3 months). Assuming a 48-month accrual period and a 12-month follow-up, 350 patients and 310 events (progressions or deaths without PD) were required.

Safety analysis was based on the population of all treated patients (at least one cycle). Time to event data (PFS, OS) were described using the Kaplan-Meier curves and compared by a stratified logrank test (at a significance level of 5%). Ninety-five percent confidence intervals (95% CI) were calculated by non-parametric methods. Estimated hazard ratios (HRs) and their 95% CI were calculated using the Cox proportional hazard model. The ORR (CR+PR) was calculated with an exact 95% CI using standard methods based on binomial distribution. Non-interim efficacy analysis was planned. All P-values were based on two-sided testing and statistical analyses were carried out using SAS statistical software version 9.3 (SAS Inc., Cary, NC).

results

patients and treatment exposure

Between 14 November 2007 and 6 March 2012, 376 patients were randomized from 17 Italian study sites. Six (1.6%) patients (three from each arm) were excluded from the analysis (five due to consent withdrawal and one due to eligibility criteria violation). Table 1 shows baseline patient characteristics, which were well balanced between the treatment groups. Comorbidities were present in ~60% of patients across both treatment groups and included cardiovascular, gastrointestinal and endocrine diseases (data not shown).
efficacy
The data cut-off for both efficacy and safety analyses was 31 December 2013, when the median duration of follow-up was 36 months (range 1–65). The median overall duration of CT treatment was 6 months in both treatment groups. Arm A patients received a median of 12 CT treatment cycles [range 1–43, inter-quartile range (IQR) 6–16] and arm B patients, a median of 11.5 (range 1–28, IQR 6–12). Forty-five arm A patients received B alone as maintenance treatment for a median of 6 cycles (range 1–30, IQR 3–13). The reasons for treatment discontinuation are reported in Figure 1.

At the data cut-off, 343 (92.7%) events had occurred for PFS (306 disease progressions and 37 deaths without progression), 163 (92.6%) in arm A and 180 (92.8%) in arm B. The median PFS was 9.6 (95% CI 8.2–10.3) and 8.4 (95% CI 7.2–9.0) months for arms A and B, respectively, with an HR of 0.86 (95% CI 0.70–1.07, P = 0.182) (Figure 2A) adjusted by center, CT regimen (FOLFOX4 or FOLFIRI) and KRAS status, and an adjusted HR (adjHR) of 0.83 (95% CI 0.67–1.04, P = 0.103) when baseline characteristics were included in the model.

Overall, 275 patients died, 131 (74.4%) in arm A and 144 (74.2%) in arm B. The median OS was 20.8 (95% CI 15.9–23.2) and 21.3 (95% CI 19.9–24.1) months for arms A and B, respectively, with an HR of 1.13 (95% CI 0.89–1.43, P = 0.317) (Figure 2B) adjusted by center and CT regimen and KRAS status and an adjHR of 1.13 (0.89–1.44, P = 0.304) when baseline characteristics were considered.

With regard to ORR, 89 (50.6%, 95% CI 43.2%–58.0%) patients were considered responders (CR+PR) in arm A and 97 (50.0%, 95% CI 43.0%–57.0%) in arm B (P = 0.865). Thirty-three (18.7%) patients in arm A and 36 (18.6%) in arm B underwent surgery for metastatic disease. Treatment effects were consistent across pre-specified subgroups defined according to age, sex, ECOG PS, prior adjuvant therapy and site of primary tumor (Figure 3). PFS, ORR and OS according to the CT regimen and KRAS status are shown in supplementary Table S1, available at Annals of Oncology online.

Following progression, 48 arm A patients with wild-type KRAS were randomized on to the second-line study, while 30 with mutated KRAS received an alternative study CT combination. In arm B, 56 patients with wild-type KRAS were randomized on to a second-line study, while 40 with mutated KRAS received an alternative study CT combination. Data are currently being collected on the second-line treatment, including results for 196 patients not enrolled on to ITACa second-line trials.

safety
Table 2 reports the most frequent adverse events observed during the assigned treatment. Hematologic toxicity was similar in both arms. We observed a higher incidence of grade ≥3 fatigue (10.3% versus 3.1%, P = 0.031) and of adverse events typically associated with B in arm A patients: in particular, hemorrhage (17% versus 4.6%, P = 0.0001), hypertension (27.8% versus 10.8%, P < 0.0001), proteinuria (22.2% versus 13.4%, P = 0.027) and thrombosis (21% versus 12.9%, P = 0.037). The incidence of grade 3–4 B-related toxicities was low.

Unacceptable toxicity leading to treatment discontinuation occurred in 30 patients (17.0%) treated with CT plus B and in 25 (12.9%) treated with CT only. Adverse events were the cause of death in 4 (2.3%) patients in the B plus CT group: sepsis associated with grade 4 neutropenia (1 patient), neutropenic colitis (1), severe anemia and anasarca (1) and pulmonary embolism (1). No toxic deaths occurred in the CT arm and no other clinically relevant or unexpected adverse events were observed (supplementary Table S2, available at Annals of Oncology online).

discussion
This phase III multicenter randomized trial failed to show a clinical benefit of adding B to FOLFOX4 or FOLFIRI in first-line treatment of mCRC patients. Our trial was designed to test the hypothesis of a minimum absolute increase of 3 months in PFS when B was added to an optimal standard CT. PFS was 9.6 for arm A and 8.4 for arm B, with an HR of 0.86 (95% CI 0.70–1.07, P = 0.182).

In the pivotal AVF2107 study, Hurwitz et al. [6] evaluated the IFL regimen with or without B in a first-line setting. The addition of B led to a significant increase in PFS (10.6 versus 6.2 months) and OS (20.3 versus 15.6 months). However, a small single-center trial by Stathopoulos et al. [10] did not reveal any difference in OS (22.0 versus 25.0 months) when B was added to a similar bolus regimen of irinotecan and 5FU. Although the entire scientific community is unanimous in not acknowledging the IFL scheme as first-line standard CT for mCRC, B has been widely accepted as an effective therapeutic option. Subsequently, some
phase III RCTs tested the efficacy of B added to first-line standard CT, with, however, conflicting results. To date, no randomized trials have been published comparing FOLFIRI and FOLFIRI + B, and only one trial has evaluated the impact of B added to oxaliplatin-based first-line CT (NO16966) [11]. The study in question by Saltz et al. (XELOX or FOLFOX4 + B in first-line mCRC) reported a statistically significant improvement in PFS (9.4 versus 8.0 months) but not in OS (21.3 versus 19.9 months) for the B-containing arm. A subset analysis demonstrated a significant improvement in PFS with B in the XELOX subgroup (HR 0.77; 95% CI 0.63–0.94; P = 0.0026) but not when FOLFOX4 was added (HR 0.89; 95% CI 0.73–1.08; P = 0.1871). Trials using B combined only with fluoropyrimidines demonstrated a significant increase in PFS (but not in OS) [7–9]. More recently, data from the TML study highlighted a small but significant improvement in OS from the use of second-line B after failure of a B-containing first-line regimen [16]. However, in the KRAS subgroup analysis, the benefit in OS (primary end point) obtained with B after progression was restricted to KRAS wt patients, with an anti-EGFR treatment administered in 76% of the population. The benefit was thus possibly related to the third-line treatment rather than to B as it was not observed in the KRAS-mutated population [16].

Preliminary results from the CALGB/SWOG 80405 study did not reveal any difference in OS (primary end point) between the bevacizumab/CT (FOLFIRI or mFOLFOX6) and cetuximab/CT (FOLFIRI or mFOLFOX6) arms. The median OS was more than 30 months. Although there was no difference in PFS, a higher ORR was observed in the cetuximab arm (68.6% versus 53.6%, P < 0.01) [17]. Similarly, an independent radiological evaluation of ORR (primary end point) of the FIRE-3 study revealed that FOLFIRI plus cetuximab induced a significantly higher ORR, tumor shrinkage rate and depth of response than FOLFIRI plus B. OS was also better in the cetuximab arm, 33.1 versus 25.0 months (HR 0.697, P = 0.0059) [18]. These data cast further doubts on the role of B in the first-line setting, at least in a RAS wild-type population. PFS in both trials was around 10 months in either arm, similar to that reported in the present study.

The choice of CT regimen was left to the discretion of our investigators, as per normal clinical practice and in line with the WJOG4407G trial, confirming the equivalence of FOLFIRI and FOFOX as first-line backbone CT in combination with B [19]. Although the optimal duration of CT remains unclear, recent data from randomized trials indicate that maintenance with B with fluoropyrimidines may be associated with a superior outcome. In our trial, treatment was continued until disease progression or unacceptable toxicity occurred. The majority of CT+B arm patients who stopped CT due to toxicity continued with B alone, which at that time was considered a good option for maintenance therapy, until progression. The discontinuation of B and/or fluoropyrimidines at the patient’s request or at the decision of the investigator may have weakened the contribution of B, explaining in part its low impact on survival in our trial.

We are fully aware that the main weakness of our study is its limited sample size and that attainment of the planned recruitment based on the original primary aim (OS) would have provided stronger evidence of the real role of B in the treatment strategy of mCRC. The work, independently funded by AIFA,
Figure 2. Kaplan–Meier estimate of progression-free survival (A) and overall survival (B). PFS, progression-free survival; HR, hazard ratio; OS, overall survival.
was aimed at improving clinical practice and a 3-year planned recruitment of 1000 patients seemed feasible when the study was designed. However, only 17 of the 30 participating centers had begun enrolment after 2 years. In accordance with AIFA recommendations, it was decided to extend the recruitment period by a maximum of 1 year and to change the primary objective to PFS rather than OS as the power of the study would not be sufficient to test the original hypothesis. In February 2011, when 211 patients had been recruited, the protocol was amended and the sample size was recalculated to guarantee sufficient power to identify a 3-month absolute difference in PFS between the two arms. Obviously, this decision was made without having analyzed any of the study data. Notwithstanding the reduction in sample size, we believe that the results from the present study can be considered of scientific value, especially, in light of recent reports indicating PFS as a potential surrogate end point of OS in mCRC [20, 21].

The final OS analysis did not reveal any difference between the study arms (HR 1.20, \( P = 0.147 \)). ORR was not affected by B, in agreement with results from other trials. Toxicity was as expected and highly manageable; in particular, toxic deaths and side-effects related to B were similar to those reported in previous trials.

In conclusion, the ITACa trial failed to show an advantage in terms of PFS from the addition of B to FOLFOX4 or FOLFIRI as first-line treatment of mCRC patients. These data confirm our initial hypothesis, i.e. if standard CT regimens are used as the backbone of therapy rather than IFL or fluoropyrimidines alone, the use of B adds little in terms of clinical benefit, especially in an unselected population with heterogeneous biological characteristics. Further research is warranted to identify the biological markers that are predictive of sensitivity to anti-angiogenic drugs.

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disclosure
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