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Original Research

Phase II randomised study of maintenance treatment with bevacizumab or bevacizumab plus metronomic chemotherapy after first-line induction with FOLFOXIRI plus Bevacizumab for metastatic colorectal cancer patients: the MOMA trial

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KEYWORDS
Metastatic colorectal cancer;
Maintenance;
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Metronomic chemotherapy

Abstract ***Background:*** Alternating induction and maintenance phases is a common strategy in metastatic colorectal cancer (mCRC). Metronomic chemotherapy (metroCT) may represent a well-tolerated chemotherapy backbone for maximising bevacizumab effect during maintenance. The MOMA trial was designed to compare metroCT plus bevacizumab versus bevacizumab alone as maintenance following 4 months of induction with FOLFOXIRI plus bevacizumab.

Patients and methods: In this phase II study, patients with unresectable mCRC were randomised to receive up to 8 cycles of FOLFOXIRI plus bevacizumab, followed by bevacizumab (arm A) or the same regimen followed by bevacizumab plus metroCT (capecitabine 500 mg/three times per day and cyclophosphamide 50 mg/die, arm B) until disease progression. The primary end-point was progression-free survival (PFS). According to the Rubinstein and Korn's design, to detect a hazard ratio[HR] of 0.75 favouring arm B, with 1 sided-alpha and beta errors of 15% and 80%, 173 events and 222 patients were required.

Results: Between May 2012 and March 2015, 232 patients, mostly with *RAS* (65%) or *BRAF* (9%) mutant tumours, were randomised in 16 Italian centres.

At a median follow-up of 47.8 months, 210 and 164 progression and death events were registered. The primary end-point was not met. Median PFS was 10.3 and 9.4 months in arm B and A, respectively (HR: 0.94 [70% confidence interval {CI}: 0.82–1.09], p = 0.680). No significant differences were reported in terms of overall survival (OS) (median OS arm B/A: 22.5/28 months; HR: 1.16 [95%CI: 0.99–1.37], p = 0.336).

Response rate with FOLFOXIRI plus bevacizumab was 63% (arm B/A: 58%/68%). In the liver-limited subgroup, the secondary resection rate was 49% (arm B/A: 45%/55%).

Conclusions: The addition of metroCT to maintenance with bevacizumab does not significantly improve PFS of mCRC patients. The activity of FOLFOXIRI plus bevacizumab is confirmed in a population with high prevalence of *RAS*/*BRAF* mutations treated with a 4-months induction.

Trial registration: www.clinicaltrials.gov NCT02271464.

1. Introduction

Alternating induction phases and maintenance periods or treatment breaks is a frequent strategy in the management of metastatic colorectal cancer (mCRC) patients. In fact, while the continuation of the first-line treatment until the evidence of disease progression was historically the common approach in clinical trials and daily practice, several studies investigated how limiting the duration of intensive regimens while not compromising treatments' efficacy both in the chemotherapy and in the targeted agents' era [1–9]. With specific regard to the best treatment option following an upfront therapy with chemotherapy plus bevacizumab, the phase II randomised MACRO trial showed that interrupting chemotherapy while continuing bevacizumab was not inferior than continuing the whole treatment until disease progression [5].

Clinical studies evaluating the relative impact of maintenance with bevacizumab alone or in combination with a fluoropyrimidine when compared with a treatment break evidenced a significant improvement in progression-free survival (PFS) with a less relevant magnitude of benefit in terms of overall survival (OS). Continuing a fluoropyrimidine in combination with bevacizumab, as recommended by international guidelines, is associated with a more evident clinical benefit, at the price of increased toxicities that may limit the subsequent re-introduction of chemotherapy after disease progression. Of note, an oxaliplatin-based doublet was the upfront chemotherapy backbone planned in all these studies [7–9]. Maintenance with 5-fluorouracil plus bevacizumab was scheduled in all clinical trials investigating first-line FOLFOXIRI plus bevacizumab that was recommended up to 12 cycles (around 6 months) [10–13].

The repeated and protracted administration of low doses of cytotoxic agents with no free intervals, defined as metronomic chemotherapy (metroCT), is an antineoplastic strategy with demonstrated efficacy in different malignancies and a favourable safety profile. MetroCT exerts an antiangiogenic activity, by inducing the blockade of circulating endothelial progenitor cells and the suppression of HIF-1α expression [14,15].

A synergic effect of metroCT and other antiangiogenic approaches including vascular endothelial growth factor inhibition was shown in preclinical

models [16,17]. In particular, the combination of cyclophosphamide and fluoropyrimidines demonstrated durable angiogenesis inhibition [18]. A phase II study in heavily pretreated mCRC patients showed signals of activity of low doses of uracil-tegafur (UFT) and cyclophosphamide plus celecoxib, a selective cyclooxygenase-2 inhibitor involved in angiogenesis inhibition, with a very limited toxicity profile [19].

Drawing from these considerations, the MOMA trial was designed with the purpose to compare two different strategies of treatment of mCRC, including a 4-months induction with FOLFOXIRI plus bevacizumab, followed by bevacizumab alone or bevacizumab plus metronomic capecitabine and cyclophosphamide, in terms of PFS.

2. Material and methods

MOMA (Maintenance bevacizumab Only or bevacizumab plus Metronomic chemotherapy in Advanced colorectal cancer) was a prospective, open-label, multicentre, comparative, randomised phase II study including mCRC patients recruited at 16 Italian Oncology Units. Main inclusion criteria were histologically confirmed colorectal adenocarcinoma; age between 18 and 75 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2 if age ≤70 years, or 0 if age 71–75 years; unresectable and measurable metastatic disease according to RECIST, version 1.1 [20] and adequate bone marrow, hepatic and renal function. Main exclusion criteria were previous palliative chemotherapy or biologic therapy for mCRC; adjuvant treatment with oxaliplatin completed less than 12 months before relapse; adjuvant treatment with fluoropyrimidine monotherapy completed less than 6 months before relapse and peripheral neuropathy of grade 2 or higher according to common terminology criteria for adverse events (CTCAE), version 4.0 [21].

Patients were randomly assigned in a 1:1 ratio to receive up to 8 cycles of induction treatment with FOLFOXIRI plus bevacizumab, followed by maintenance with bevacizumab (arm A) or bevacizumab plus metroCT (arm B) until tumour progression, unacceptable toxicity or patient's refusal.

Patients in both arms received bevacizumab at dose of 5 mg/kg intravenous infusion (iv) plus FOLFOXIRI, consisting of irinotecan 165 mg/m^2 iv, followed by oxaliplatin 85 mg/m^2 iv given concurrently with L-leucovorin at a dose of 200 mg/m^2, followed by fluorouracil 3200 mg/m^2 for 48 h continuous infusion. Treatment cycles were repeated every 14 days up to 8 cycles. Thereafter, maintenance treatment with bevacizumab (7.5 mg/kg iv) or bevacizumab (7.5 mg/kg) plus metroCT (capecitabine 500 mg three times/day and cyclophosphamide 50 mg/day) was planned for arm A and B, respectively, with cycles repeated every 21 days, until progressive disease, patient's refusal, unacceptable toxic effects or consent withdrawal.

If disease progression occurred during maintenance therapy with no unacceptable toxicity, the reintroduction of FOLFOXIRI plus bevacizumab for four cycles, followed by maintenance according to the randomisation arm was planned.

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 computed tomography scans repeated every 8 weeks.

The primary end-point was PFS, defined as the time from randomisation to first documentation of objective disease progression or death due to any cause, whichever occurs first. Secondary end-points included OS, response rate (RR), resection rate and rate of adverse events.

RAS and *BRAF* status was centrally assessed on primary tumours or related metastases by means of mass spectrometry using the matrix-assisted laser desorption ionisation-time of flight MassARRAY system (Sequenom, San Diego, CA, USA) at the Department of Surgical, Medical and Molecular Pathology and Critical Care Medicine of the University of Pisa [22,23].

2.1. Statistical analyses

According to the Rubinstein and Korn design, considering a power of 80% and a 1-sided type-I error of 15%, 173 events were required to detect a hazard ratio (HR) of 0.75 for PFS in favour of the addition of metroCT.

PFS results were summarised using the Kaplan-Meier method; HRs and corresponding 70% confidence intervals (CIs) were estimated with the Cox proportional hazard regression model.

Also, OS results were summarised using the Kaplan-Meier method; HRs and corresponding 95% CIs were estimated. The median period of follow-up was calculated for the entire study cohort according to the reverse Kaplan–Meier method.

The objective RR and the rate of 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.

Analyses concerning activity and efficacy outcomes were performed in the intention-to-treat (ITT) population, including all randomised patients, while toxicity parameters were investigated in the safety population, including all those patients who had received at least one cycle.

3. Results

From May 30th, 2012 to March 30th, 2015, 232 patients from 16 Italian centres were randomly assigned to

FOLFOXIRI plus bevacizumab followed by maintenance with bevacizumab (n = 117, arm A) or FOLFOXIRI plus bevacizumab followed by maintenance with bevacizumab plus metroCT (n = 115, arm B). One patient in arm A did not receive any cycle of treatment according to random assignment and therefore was not included in the safety population (Fig. 1).

The study population was balanced at baseline between the two arms (Table 1). Altogether, 85% of patients had an ECOG PS of 0, 82% presented with synchronous metastases, 44% had an unresected primary tumour and 11% had previously received an adjuvant treatment; 56% of patients had multiple sites of metastases, and 31% had liver-limited disease. According to the central assessment, *RAS* and *BRAF* were found mutated the 65% and 9% of cases, respectively, while the 15% of tumours were *RAS*/*BRAF* wt, and the remaining 11% were not evaluable.

231 patients were included in the safety population. The median number of cycles administered per patient as induction treatment was eight (range, 1–12), and the average relative dose intensities for fluorouracil, irinotecan, oxaliplatin and bevacizumab were 94%, 91%, 95% and 94%, respectively.

The incidence of grade 3–4 adverse events was similar in the two arms (Table 2). Grade 3–4 neutropenia occurred in the 55% of patients, while 11.3% experienced febrile neutropenia. Diarrhoea (13.4%), asthenia (10.8%), stomatitis (3.9%), anorexia (5.2%) and hypertension (3.5%) were the most frequent grade 3–4 non-haematological adverse events.

After the induction phase, a total of 165 patients were candidate to maintenance therapy; 88 (75%) patients in arm A and 77 (67%) patients in arm B received at least one cycle of maintenance therapy.

In the overall population, 66 patients did not receive any cycle of maintenance because of the following reasons: death (N = 8), disease progression before starting maintenance (N = 21), medical decision (N = 16), patient's refusal (N = 7), toxicity due to bevacizumab (N = 5) and other reasons (N = 9) (Fig. 1). A median number of seven cycles (range, 1–63) of maintenance was administered, and grade 3–4 adverse events were rare (Table 2); only the incidence of hand & foot syndrome was significantly higher in the bevacizumab plus metroCT group (p = 0.004).

The proportion of patients who achieved objective response with FOLFOXIRI plus bevacizumab was 63%

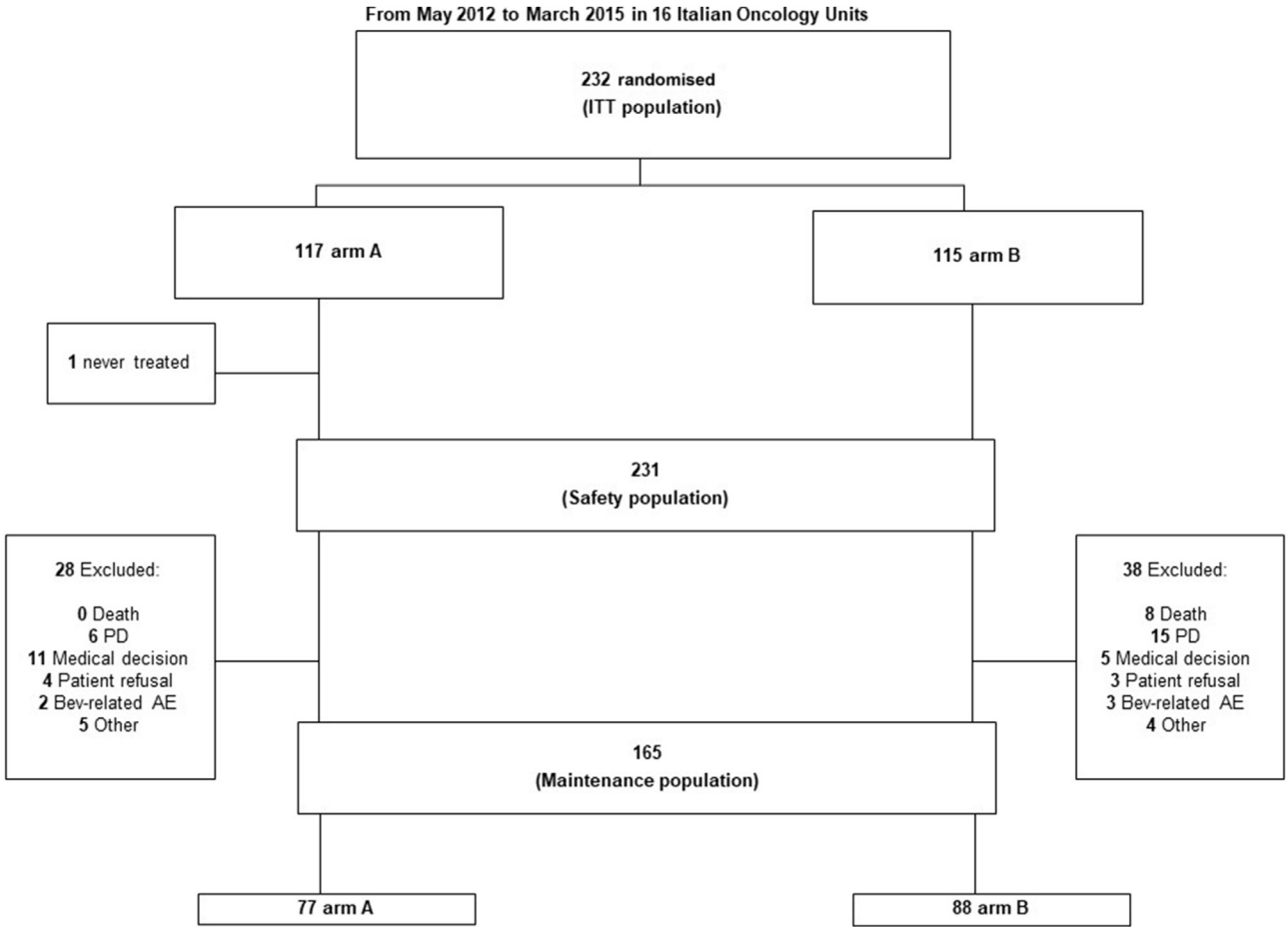

Fig. 1. MOMA study CONSORT diagram. PD, progressive disease; AE, adverse event.

Table 1
Main demographic and clinical characteristics of patients in the ITT population.

Characteristic, N (%)	bev (N = 117)	bev + metroCT (N = 115)	ITT population (N = 232)
Age (years)	61 (23–74)	62 (31–74)	61 (23–74)
Sex			
Male	71 (61%)	64 (56%)	135 (58%)
Female	46 (39%)	51 (44%)	97 (42%)
ECOG PS			
0	99 (85%)	99 (86%)	198 (85%)
1–2	18 (15%)	16 (14%)	34 (15%)
Synchronous metastases			
Yes	95 (81%)	95 (83%)	190 (82%)
No	22 (19%)	20 (17%)	42 (18%)
Prior adjuvant chemotherapy			
Yes	16 (14%)	10 (9%)	26 (11%)
No	101 (86%)	105 (91%)	206 (89%)
Primary tumour site			
Right	38 (32,5%)	48 (42%)	86 (37%)
Left	38 (32,5%)	37 (32%)	75 (32%)
Rectum	41 (35%)	30 (26%)	71 (31%)
Number of metastatic sites			
1	43 (37%)	58 (50%)	101 (44%)
>1	74 (63%)	57 (50%)	131 (56%)
Liver-only disease			
Yes	33 (28%)	40 (35%)	73 (31%)
No	84 (72%)	75 (65%)	159 (69%)
Resected primary tumour			
Yes	69 (59%)	61 (53%)	130 (56%)
No	48 (41%)	54 (47%)	102 (44%)
Mutational status			
RAS/*BRAF* wt	21 (18%)	15 (15%)	36 (15%)
RAS mut	77 (66%)	73 (63%)	150 (65%)
BRAF mut	8 (7%)	12 (10%)	20 (9%)
NE	11 (9%)	15 (14%)	26 (11%)

NE, not evaluated; ECOG PS, Eastern Cooperative Oncology Group performance status; bev, bevacizumab; metroCT, metronomic chemotherapy.

Table 2
Grade ≥3 treatment-related adverse events occurring in at least 3% of patients.

G3/4 adverse events, %	Induction phase		Overall N = 231
	bev (N = 116)	bev + metroCT (N = 115)	
Nausea	2.6%	3.5%	3.0%
Vomiting	0.9%	6.1%	3.5%
Diarrhoea	11.2%	15.6%	13.4%
Stomatitis	3.5%	4.4%	3.9%
Neutropenia	59.5%	50.4%	55.0%
Febrile neutropenia	13.8%	8.7%	11.3%
Neurotoxicity	0.9%	1.7%	1.3%
Asthenia	12.9%	8.7%	10.8%
Anorexia	4.3%	6.1%	5.2%
Hypertension	5.2%	1.7%	3.5%
Venous thromboembolism	1.7%	5.2%	3.5%
G3/4 adverse events, %	**Maintenance phase**		**p**
	bev (N = 88)	bev + metroCT (N = 77)	
Hand-foot syndrome	0	9.1	0.004
Neutropenia	0	3.9%	NS
Hypertension	4.5%	3.9%	NS

bev, bevacizumab; metroCT, metronomic chemotherapy.

in the overall population (arm B/A: 58%/68%, p = 0.103) (Supplementary Table S1). In terms of R0 secondary surgery on metastatic sites, the resection rate was 17% in the overall population and 34% in the liver-only subgroup, with no differences between the two arms (Supplementary Table S1).

At a median follow-up of 47.8 months (interquartile range: 36.2–55.3), the PFS analysis was based on 210 events (91%) out of 232 patients, 104 and 106 in arm A and B, respectively. Median PFS was 10.3 (70% CI:9.1–11.6) months in arm B and 9.4 (70% CI: 8.3–10.6) months in arm A (HR: 0.94 [70% CI: 0.82–1.09], p = 0.680) (Fig. 2A). No interaction effect was evident between treatment groups and investigated clinical and molecular factors, including *RAS*/*BRAF* status and primary tumour location (Supplementary Fig. S1).

One hundred and sixty-four (71%) out of 232 patients died, 85 (73%) and 79 (69%) in arm A and B, respectively. Median OS was 22.5 (95% CI: 18.4–25.8) months in arm B and 28.0 (95% CI: 20.0–33.6) months in arm A (HR:1.16, [95% CI: 0.99–1.37], p = 0.336) (Fig. 2B).

Out of 210 patients who experienced disease progression, 152 (72%) received a treatment after progression. Among them, 91 (60%) received the reintroduction with FOLFOXIRI plus bevacizumab, and 47 (24%) received a doublet (FOLFIRI/FOLFOX) with or without bevacizumab (Supplementary Table S2).

No impact of *RAS*/*BRAF* status or tumour sidedness on OS was evident in the overall population. Median OS was 31.3 months (95% CI: 15.6–45.8) in the *RAS*/*BRAF* wild-type subgroup compared with 24.9 months (95% CI: 12.4–45.3) in the *RAS* mutant subgroup (HR: 1.20 [95% CI: 0.77–1.87], *p* = 0.414) and 19.2 months (95% CI: 11.5–35.2) in the *BRAF* mutant subgroup (HR: 1.52 [95% CI: 0.79–2.89], p = 0.208).

Similarly, median OS was 25.4 months (95% CI: 13.7–43.1) in the left-colon group compared with 23.0 months (95% CI: 12.5–45.3) in the right-colon group (HR: 0.90 [95% CI: 0.66–1.24], p = 0.522) (Supplementary Table S3).

4. Discussion

Limiting the duration of the upfront chemotherapy to a short induction period, then exploiting maintenance to prolong disease control as long as possible at the price of a reasonable toxicity profile, is an appealing strategy for mCRC patients. In this perspective, no more than 12 cycles of treatment were planned in trials evaluating

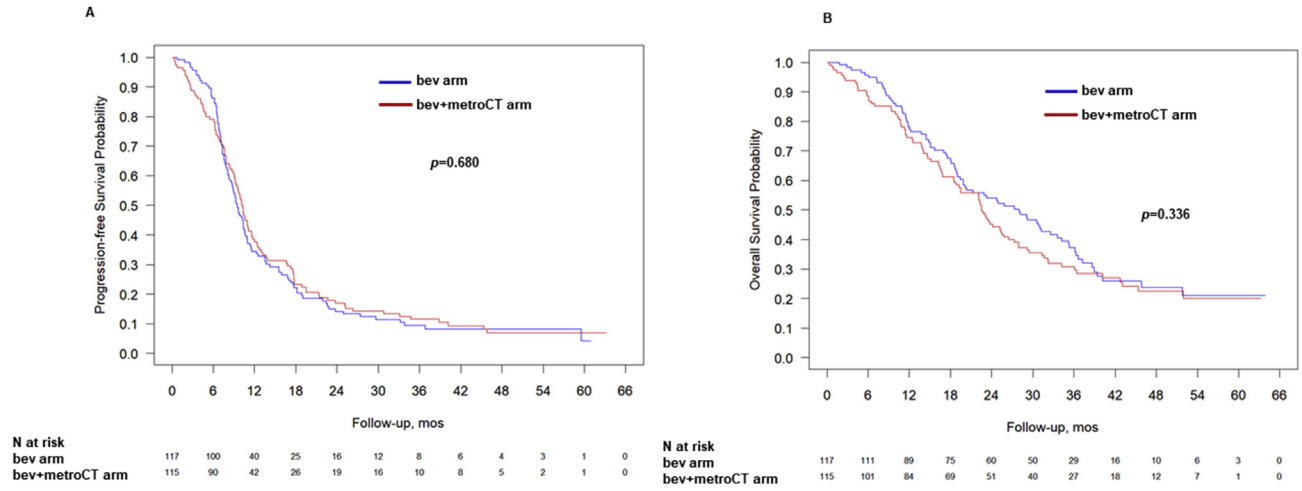

Fig. 2. Kaplan-Meier estimates of PFS (A) and OS (B) according to treatment arm. Bev, bevacizumab; metroCT, metronomic chemotherapy; PFS, progression-free survival; OS, overall survival.

FOLFOXIRI as upfront regimen, both alone and in combination with targeted agents.

These concepts were emphasised in the design of the MOMA study, where a shortened induction phase, limited to 8 instead of 12 cycles, was planned, followed by two different maintenance strategies. Indeed, the efficacy of adding metroCT to bevacizumab to extend 'full chemotherapy'-free interval was evaluated.

The choice of bevacizumab alone as control arm was driven by the intent to offer a chemotherapy-free interval after the induction phase. In the light of results from randomised trials that led to identify fluoropyrimidines plus bevacizumab as the preferred maintenance option after upfront chemotherapy plus bevacizumab [7–9] that became available during the conduction of the MOMA trial—this choice is a clear limitation of the study design. Indeed, bevacizumab alone is not a standard maintenance option, and recent results from the PRODIGE 9 study confirmed the lack of efficacy of this approach [24].

The primary end-point of the MOMA study was not met: the addition of metroCT failed to prolong PFS. Another study, CAIRO-3, investigated the impact of 'low dose' capecitabine plus bevacizumab versus observation, showing a significant impact in terms of PFS and PFS2, and a borderline significant OS benefit. However, in that study, capecitabine was administered at 625 mg/sqm/bid continuously, corresponding to the 93.8% of the dose intensity of a full-dose capecitabine administered at 1000 mg/sqm/bid dd1→14 every 21 days.

Therefore, putting our findings in the context of available evidence in the field of maintenance, the combination of a full dose fluoropyrimidine plus bevacizumab is confirmed as the best option following first-line chemotherapy plus bevacizumab. With specific regard to trials investigating upfront FOLFOXIRI plus bevacizumab, maintenance with 5FU/LV plus bevacizumab was planned until disease progression, so that it should be considered part of the first-line strategy.

Differently from other clinical trials addressing the issue of maintenance, in the MOMA study, patients were randomised at the beginning instead of at the end of the induction treatment. This choice was coherent with the objective to evaluate not only two different maintenance treatments but also to investigate the whole strategies of administering a shortened first-line combination therapy, followed by a 'no-chemo' or 'very light chemo' period. As a consequence, 28% of enrolled patients never received maintenance, thus reducing the power to detect a difference in PFS due to the addition of metroCT to bevacizumab. Taking into account the lower power due to the limited size of the maintenance population, present results should be cautiously interpreted.

Similarly, unbalances between the two groups in terms of prognostic characteristics of patients actually exposed to maintenance may have occurred. As an example, a higher percentage of patients in the bevacizumab alone than in the bevacizumab plus metroCT arm had experienced response during induction.

On the other side, the upfront randomisation allowed us to get additional data, corroborating activity and safety results of FOLFOXIRI plus bevacizumab as initial therapy for mCRC patients. An overall 63% RR was achieved in a population at poor prognosis because of the high prevalence of *RAS* and *BRAF* mutant tumours (around 75%), with consistent results also in terms of PFS. Shorter median OS was registered in the MOMA trial when compared with the previous TRIBE study. A potential explanation may be that patients included in the MOMA study received less chemotherapy in their therapeutic strategy when compared with those included in TRIBE. In fact, they received no

5FU/LV during maintenance, and after progression, the reintroduction of FOLFOXIRI or a modified FOLFOXIRI schedule only up to 4 cycles was recommended and actually chosen in most patients, then followed again by a maintenance treatment not including 5FU/LV. Preliminary results of the TRIBE2 study (NCT02339116), achieved in a population of 679 mCRC patients with molecular characteristics similar to those of the MOMA population and treated with 4-months induction, are highly consistent with those reported in TRIBE in terms of RR and PFS, as well as with regard to the magnitude of the benefit provided by the intensification of the chemotherapy backbone, while OS results are not mature yet [25].

Notably, outcome results reported in the MOMA study among patients with *BRAF* mutant tumours and among those with right-sided ones, both associated with poor prognosis, are consistent with previous experiences with FOLFOXIRI plus bevacizumab and favourably compare with literature data with first-line doublets plus a targeted agent.

More patients treated with bevacizumab alone received a second-line therapy, probably as a consequence of the modest but higher incidence of chemotherapy-related adverse events in the metroCT arm.

5. Conclusions

The MOMA study did not meet its primary end-point of demonstrating an increase in PFS with the addition of metroCT to bevacizumab during maintenance. Taking together available evidence, 5FU/LV plus bevacizumab should remain the standard maintenance option following upfront FOLFOXIRI plus bevacizumab.

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Conflict of interest statement

Dr Cremolini reported receiving personal fees from F. Hoffman– La Roche, Bayer, Sirtex, and Amgen. Prof. Falcone reported receiving grants and personal fees from F. Hoffman–La Roche, Amgen, and Merck Serono as well as personal fees from Celgene, Bayer, and Sanofi Aventis. Dr Masi has received personal fees from Amgen, F Hoffman-La Roche, Bayer, Merk Serono and Sirtex.

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Dr Cremolini and Dr Marmorino contributed equally. Dr Falcone had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The authors are grateful to all participating patients, their families and their caregivers as well as to the GONO investigators from all participating oncology units in Italy.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.12.028.

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