original reports

Individual Patient Data Meta-Analysis of FOLFOXIRI Plus Bevacizumab Versus Doublets Plus Bevacizumab as Initial Therapy of Unresectable Metastatic Colorectal Cancer

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abstract

PURPOSE A proper estimation of the magnitude of the overall survival (OS) benefit from infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) plus bevacizumab versus doublets + bevacizumab is lacking because all trials that have investigated this regimen had primary end points other than OS. To test OS with higher power and to explore the interaction of treatment effect with main patient and disease characteristics, we performed an individual patient data (IPD) meta-analysis.

PATIENTS AND METHODS IPD from 5 eligible trials were collected: CHARTA (ClinicalTrials.gov identifier: NCT01321957), OLIVIA (ClinicalTrials.gov identifier: NCT00778102), STEAM (ClinicalTrials.gov identifier: NCT01765582), TRIBE (ClinicalTrials.gov identifier: NCT00719797), and TRIBE2 (ClinicalTrials.gov identifier: NCT02339116). The primary end point was OS. Secondary end points were progression-free survival (PFS), objective response rate (ORR), R0 resection rate, grade 3/4 adverse events, and subgroup analyses according to clinical and molecular characteristics.

RESULTS A total of 1,697 patients were randomly assigned to FOLFOXIRI + bevacizumab (n = 846) or doublets + bevacizumab (n = 851). Most (78%) had an Eastern Cooperative Oncology Group performance status of 0, and the median age was 61 years. After a median follow-up of 39.9 months, patients assigned to FOLFOXIRI + bevacizumab had significantly longer OS than those assigned to doublets + bevacizumab (median, 28.9 *v* 24.5 months; hazard ratio [HR], 0.81; 95% CI, 0.72 to 0.91; $P < .001$), with no significant heterogeneity among trials ($P = .39$; $I^2 = 2\%$). No significant interaction effect between treatment arm and investigated characteristics was demonstrated. Patients assigned to FOLFOXIRI + bevacizumab had longer PFS (median, 12.2 *v* 9.9 months; HR, 0.74; 95% CI, 0.67 to 0.82; $P < .001$), higher ORR (64.5% *v* 53.6%; $P < .001$), higher R0 resection rate (16.4% *v* 11.8%; $P = .007$), and higher rates of grade 3/4 neutropenia (45.8% *v* 21.5%; $P < .001$), febrile neutropenia (6.3% *v* 3.7%; $P = .019$), and diarrhea (17.8% *v* 8.4%; $P < .001$).

CONCLUSION FOLFOXIRI + bevacizumab significantly and meaningfully improves survival of patients with metastatic colorectal cancer compared with doublets + bevacizumab and provides advantage in PFS, ORR, and R0 resection rate at the price of a moderate increase in toxicity. No increased benefit is observed among patients with *BRAF*-mutant tumors.

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ASSOCIATED CONTENT

Data Supplement

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INTRODUCTION

In the past 10 years, the choice of first-line therapy for patients with metastatic colorectal cancer (mCRC) has been made more complex by the increased availability of different treatment options. The anti-angiogenic bevacizumab and the anti–epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab and panitumumab (only for patients with *RAS* wild-type tumors) entered the therapeutic scenario, and different intensities of the first-line chemotherapy backbone were investigated, spanning from 1 to 3 active cytotoxics.[1-4]

A phase III randomized trial by Gruppo Oncologico del Nord Ovest demonstrated the superiority of an intensified regimen, the triplet FOLFOXIRI (irinotecan 165 mg/m^2, oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, and fluorouracil 3,200 mg/m^2 48-hour continuous infusion) over an irinotecan-based doublet as upfront therapy of patients with mCRC.[5] The trial was conducted when the role of targeted agents in this setting had not yet been well established.

More recently, several phase II and III randomized trials compared the triplet FOLFOXIRI with chemotherapy

CONTEXT

Key Objective

To estimate the magnitude of benefit of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) + bevacizumab versus doublets + bevacizumab as first-line therapy for patients with unresectable metastatic colorectal cancer (mCRC) and to identify subgroups more likely to benefit.

Knowledge Generated

The advantage by FOLFOXIRI + bevacizumab is clinically relevant and independent of main clinical and molecular characteristics. Findings are consistent in terms of overall survival, progression-free survival, response rate, and resection rate. Higher incidence of chemotherapy-related adverse events of grade 3 or 4 is reported with FOLFOXIRI + bevacizumab. No increased benefit among patients with *BRAF*-mutant tumors is evident.

Relevance

FOLFOXIRI + bevacizumab is a preferred upfront option for patients with mCRC with an Eastern Cooperative Oncology Group performance status of 0-1 and right-sided and/or *RAS*-mutated unresectable tumors not previously exposed to an oxaliplatin-based adjuvant therapy, independently of the intent of conversion to resectability.

doublets (infusional fluorouracil, leucovorin, and oxaliplatin [FOLFOX] or fluorouracil, leucovorin, and irinotecan [FOLFIRI]), both in combination with bevacizumab, demonstrating that the intensification of the upfront chemotherapy was beneficial for patients with mCRC at the price of an increase incidence of some hematologic and GI adverse events.[6-12] Based on these results, FOLFOXIRI + bevacizumab is included among first-line options in most clinical guidelines and recommendations worldwide.[1-3] However, questions are still open about the proper placement of this therapeutic choice in daily practice.

First, to fully appreciate the cost/benefit balance of this option, an accurate estimation of the magnitude of the survival benefit provided by the intensification of the upfront chemotherapy is required to evaluate the acceptability of the additional toxicity. Such estimation is currently lacking because all those trials had primary end points other than overall survival (OS), and most of them were underpowered to detect a potentially relevant survival effect. Second, the identification of clinical and/or molecular characteristics associated with a higher benefit from the triplet would be helpful in properly selecting candidate patients. To this regard, FOLFOXIRI + bevacizumab is now often used in patients with *BRAF* V600E-mutated mCRC based on the post hoc subgroup analysis of the TRIBE study, but results of subgroup analyses from other trials are not consistent.[1,3,7,9,12] Based on these considerations, we conducted a systematic review followed by an individual patient data (IPD)–based meta-analysis aimed at providing a robust estimation of the added value of FOLFOXIRI + bevacizumab over conventional doublets + bevacizumab in terms of OS and at exploring the interaction of treatment effect with main patient and disease characteristics at baseline.

PATIENTS AND METHODS

Identification of Studies and Collection of Data

This systematic review and meta-analysis of IPD is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[13] The literature search was performed in January 2019 to identify all randomized clinical trials that compared doublet (ie, FOLFIRI, irinotecan and capecitabine [XELIRI], FOLFOX, capecitabine and oxaliplatin [XELOX]) versus the triplet FOLFOXIRI, both in combination with bevacizumab, as first-line treatment of patients with mCRC. The search was carried out using PubMed, Embase, Medline, Cochrane Library, ASCO proceedings, and European Society of Medical Oncology (ESMO) proceedings, without any date restrictions. The following keywords were entered in all the possible combinations: metastatic colorectal cancer, first-line, doublet, FOLFOX, FOLFIRI, XELOX, XELIRI, triplet, FOLFOXIRI, bevacizumab, and randomized controlled trial. References of the identified articles were checked, and principal investigators were asked whether they were aware of other published or unpublished trials. The following IPD at baseline were collected: age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, primary tumor sidedness, time to diagnosis of metastatic disease (synchronous *v* metachronous), previous adjuvant chemotherapy (yes *v* no) and type of adjuvant therapy (oxaliplatin *v* not oxaliplatin based), surgery on primary tumor, type of metastatic spread (involved organs at baseline), *RAS* and *BRAF* molecular status determined on tissue samples from either primary tumor or related metastases according to procedures of each study, and treatment arm (doublets + bevacizumab *v* FOLFOXIRI + bevacizumab). RECIST, secondary resection of metastases (yes *v* no) and outcome resection (R0 *v* R1 *v* R2 *v* palliative resection), first-line progression-free survival (PFS), and OS were also collected.

Study Quality

Each study was assessed for quality and potential bias using a structured checklist that was based on Method for Evaluating Research and Guideline Evidence (MERGE) criteria.[14] Quality of randomization, blinding, outcome measures, measure assessment, arm comparability, loss to follow-up, and intention-to-treat analysis were evaluated. An overall quality score was assigned to each study, as follows: A (low risk of bias), B1 (low to moderate risk of bias), B2 (moderate to high risk of bias), or C (high risk of bias).

Data were carefully checked and verified for consistency with original publications or abstracts; discrepancies were discussed and resolved with the authors before setting up the final pooled database. The approval of a formal protocol for the IPD meta-analysis was obtained from the principal investigators of all trials.

Statistical Analysis

All the efficacy analyses were done on an intention-to-treat basis. Safety was assessed in patients who received at least 1 dose of study treatment. All the analyses were stratified by trial. All tests were two-sided.

The primary end point was OS, defined as the time since study random assignment to death as a result of any cause. Secondary end points were PFS, defined as the time since study random assignment to the first evidence of disease progression or death as a result of any cause; objective response rate (ORR), defined as the percentage of patients who experienced partial or complete response according to the version of RECIST adopted in each trial; rate of R0 surgery of metastases (ie, resection with no macroscopic or microscopic residual tumor), defined as the percentage of patients of the total number of included patients who underwent an R0 resection of metastases; and rate of

TABLE 1. Characteristics of the Five Randomized Trials Included in the Meta-Analysis

Characteristic	TRIBE	OLIVIA	CHARTA	STEAM	TRIBE2
Phase of the study	III	II	II	II	III
Country	Italy	Austria, France, Spain, and United Kingdom	Germany	United States	Italy
Treatment of control arm	FOLFIRI + Bev	FOLFOX + Bev	FOLFOX + Bev	FOLFOX + Bev	FOLFOX + Bev
Primary end point	PFS	Overall resection rate	PFR at 9 months	ORR and PFS	PFS2
Planned No. of participants	(n = 450)	(n = 80)	(n = 250)	(n = 280)[a]	(n = 654)
Actual No. of participants	(N = 508)	(N = 80)	(N = 242)	(N = 280)[a]	(N = 679)
Start of the accrual	July 2008	October 2008	July 2011	January 2013	February 2015
End of the accrual	May 2011	December 2011	December 2014	December 2014	May 2017
No. of participating sites	34	16	51	45	58
Median follow-up, months	48.1	28.3	57.1	22.2	35.9
Trial quality (MERGE criteria)	B1	B1	B1	B1	B1
Eligibility criteria					
Age, years	18-75	≥ 18	≥ 18	18-75	18-75
ECOG performance status	0-2[b]	0-1	0-2	0-1[c]	0-2[b]
Previous oxaliplatin-based adjuvant therapy	Allowed	Allowed	Allowed	Allowed	Not allowed
Time between end of adjuvant therapy and relapse, months	> 12	> 6	> 6	> 12	> 6
Type of metastatic spread	Any site	Liver only	Any site	Any site	Any site
Planned treatment					
Duration of induction	Up to 6 months/ 12 cycles	Up to 6 months/12 cycles	Up to 6 months/12 cycles	Up to 4-6 months/8-12 cycles	Up to 4 months/8 cycles
Schedule of maintenance	FU and Bev	FU and Bev	FU or cape + Bev	FU or Cape + Bev	FU and Bev
RECIST version	1.0	1.0	1.1	1.1	1.1

Abbreviations: FU, fluorouracil in combination with leucovorin; Bev, bevacizumab; Cape, capecitabine; ECOG, Eastern Cooperative Oncology Group; FOLFIRI, infusional fluorouracil, leucovorin, and irinotecan; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; MERGE, Method for Evaluating Research and Guideline Evidence; ORR, overall response rate; PFR, progression-free rate; PFS, progression-free survival; PFS2, progression-free survival 2.

[a]Considering 3 arms of treatment from the original trial design.

[b]ECOG performance status 0-2 if age ≤ 70 years or 0 if age 71-75 years.

[c]ECOG performance status 0-1 if age ≤ 70 years or 0 if age 71-75 years.

TABLE 2. Baseline Patient and Tumor Characteristics of the Pooled Population (N = 1,697)

Characteristic	Group, No. (%)	
	Control (n = 851)	Experimental (n = 846)
Median age, years (IQR)	61 (53-67)	60 (53-67)
Sex		
Male	518 (61)	489 (58)
Female	333 (39)	357 (42)
ECOG performance status		
0	656 (77)	667 (79)
1	180 (21)	168 (20)
2	12 (2)	7 (1)
Missing	3	4
Time to metastasis		
Synchronous	720 (85)	716 (85)
Metachronous	130 (15)	130 (15)
Missing	1	0
Prior adjuvant chemotherapy		
No	790 (93)	782 (92)
Yes	61 (7)	63 (8)
Missing	0	1
Primary tumor site		
Right	255 (32)	295 (37)
Left	418 (53)	389 (49)
Rectum	117 (15)	107 (14)
Missing	61	55
Liver-only disease		
Yes	254 (30)	300 (36)
No	596 (70)	543 (64)
Missing data	1	3
Surgery on primary tumor		
Yes	465 (55)	445 (53)
No	386 (45)	400 (47)
Missing	0	1
RAS and *BRAF* status		
RAS and *BRAF* wild type	172 (26)	177 (27)
RAS mutated	430 (66)	422 (64)
BRAF mutated	54 (8)	61 (9)
Missing	195	186
Primary tumor site and *RAS* and *BRAF* status		
Right and *RAS* and *BRAF* wild type	31 (5)	44 (7)
Right and *RAS* mutated	149 (23)	168 (26)
Right and *BRAF* mutated	40 (6)	39 (6)
Left and *RAS* and *BRAF* wild type	134 (21)	132 (20)
Left and *RAS* mutated	273 (43)	250 (38)
Left and *BRAF* mutated	13 (2)	22 (3)
Missing	211	191

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

treatment-related grade 3 or 4 adverse events, defined as the percentage of patients experiencing grade 3 or 4 all-cause adverse events of the total number of patients eligible for toxicity analysis. Prespecified subgroup analyses of OS and PFS were performed to explore the consistency of the treatment effect on the outcome according to key patient and disease characteristics.

The median duration of follow-up and its interquartile range (IQR) were calculated according to the reverse Kaplan-Meier method. Distributions of time-to-event variables for OS and PFS were estimated with the use of the Kaplan-Meier product limit method. The log-rank test stratified by trial was used as primary analysis for comparisons between treatment groups. The heterogeneity among studies was quantified through the Higgins I^2 index. Subgroup analyses were performed by means of an interaction test. The ORR, the proportion of patients undergoing an R0 resection of metastases, and the toxicities were compared using the Mantel-Haenszel χ^2 test stratified by trial for combining 2×2 tables.

All statistical analyses on IPD were performed with SPSS version 25.0 for Windows (IBM Corporation, Chicago, IL). Trial-level meta-analysis to obtain plots for each trial and calculate the heterogeneity among studies was performed using the RevMan 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Of the 101 entries returned by our search strategy, 5 eligible trials were identified: TRIBE (ClinicalTrials.gov identifier: NCT00719797), OLIVIA (ClinicalTrials.gov identifier: NCT00778102), CHARTA (ClinicalTrials.gov identifier: NCT01321957), STEAM (ClinicalTrials.gov identifier: NCT01765582), and TRIBE2 (ClinicalTrials.gov identifier: NCT02339116).[6-10,12] One trial (METHEP-2; ClinicalTrials.gov identifier: NCT01442935) was excluded because a triple regimen other than FOLFOXIRI (ie, fluorouracil, leucovorin, irinotecan, and oxaliplatin) was used.[15] Main characteristics of each study are listed in Table 1, and their detailed eligibility criteria and results have been previously reported.[6-10,12,16]

In all studies, most of the evaluation criteria for the MERGE checklist were fulfilled, with overall quality score B1 (all included studies were of sufficiently high quality to consider the risk of bias as low to moderate). Overall, 1,705 (95%) of the 1,797 patients initially randomly assigned were eligible for the meta-analysis (92 patients were excluded because they had received an alternating treatment with doublets, named sequential FOLFOXIRI, in the STEAM trial). IPD were available for 1,697 patients (99.5%) who were included in the meta-analysis (8 patients randomly assigned in the CHARTA study had no available data and were excluded from the intention-to-treat population of the trial).

Inclusion criteria were not the same among the 5 trials. The OLIVIA trial randomly assigned only patients with disease confined to the liver; the TRIBE2 trial included only patients who had not received an oxaliplatin-containing adjuvant therapy (Table 1). In all eligible studies, an induction phase was planned, with a duration ranging from 4 to 6 months followed by maintenance with a fluoropyrimidine (fluorouracil and leucovorin or capecitabine) + bevacizumab until disease progression, patient refusal, unacceptable adverse events, or consent withdrawal (Table 1).

Of the 1,697 included patients, 851 (50.1%) were assigned to the doublets + bevacizumab group and 846 (49.9%) to the FOLFOXIRI + bevacizumab group. Patient demographic, clinical, and molecular characteristics are listed in Table 2. Among patients allocated in the doublets + bevacizumab group, 595 (69.9%) received treatment with FOLFOX + bevacizumab and 256 (30.1%) with FOLFIRI + bevacizumab. The median age of the pooled population was 61 years (IQR, 53-67 years); most patients had an ECOG performance status of 0 (78.3%) and presented with synchronous metastases (84.7%). Of the patients, 34.8% had a right-sided primary tumor, and 32.7% had liver-limited disease. Of 1,316 patients with available data, *RAS* and *BRAF* mutations were reported in 65% and 9%, respectively. No relevant differences between the 2 treatment groups were evident, except for a higher percentage of patients with a right-sided primary tumor (37.3% *v* 32.3%) and liver-only disease (35.6 *v* 29.9%) in the FOLFOXIRI + bevacizumab group (Table 2).

After a median follow-up of 39.9 months (IQR, 30.1-49.9 months)—40.8 months in the doublet + bevacizumab group and 38.9 months in the FOLFOXIRI + bevacizumab group)—1,118 (66%) of 1,697 patients died (591 [69%] in the doublets + bevacizumab group and 527 [62%] in the FOLFOXIRI + bevacizumab group). Median OS was 28.9 months (95% CI, 27.3 to 30.4 months) in the FOLFOXIRI + bevacizumab group and 24.5 months (95% CI, 23.0 to 25.9 months) in the doublets + bevacizumab group

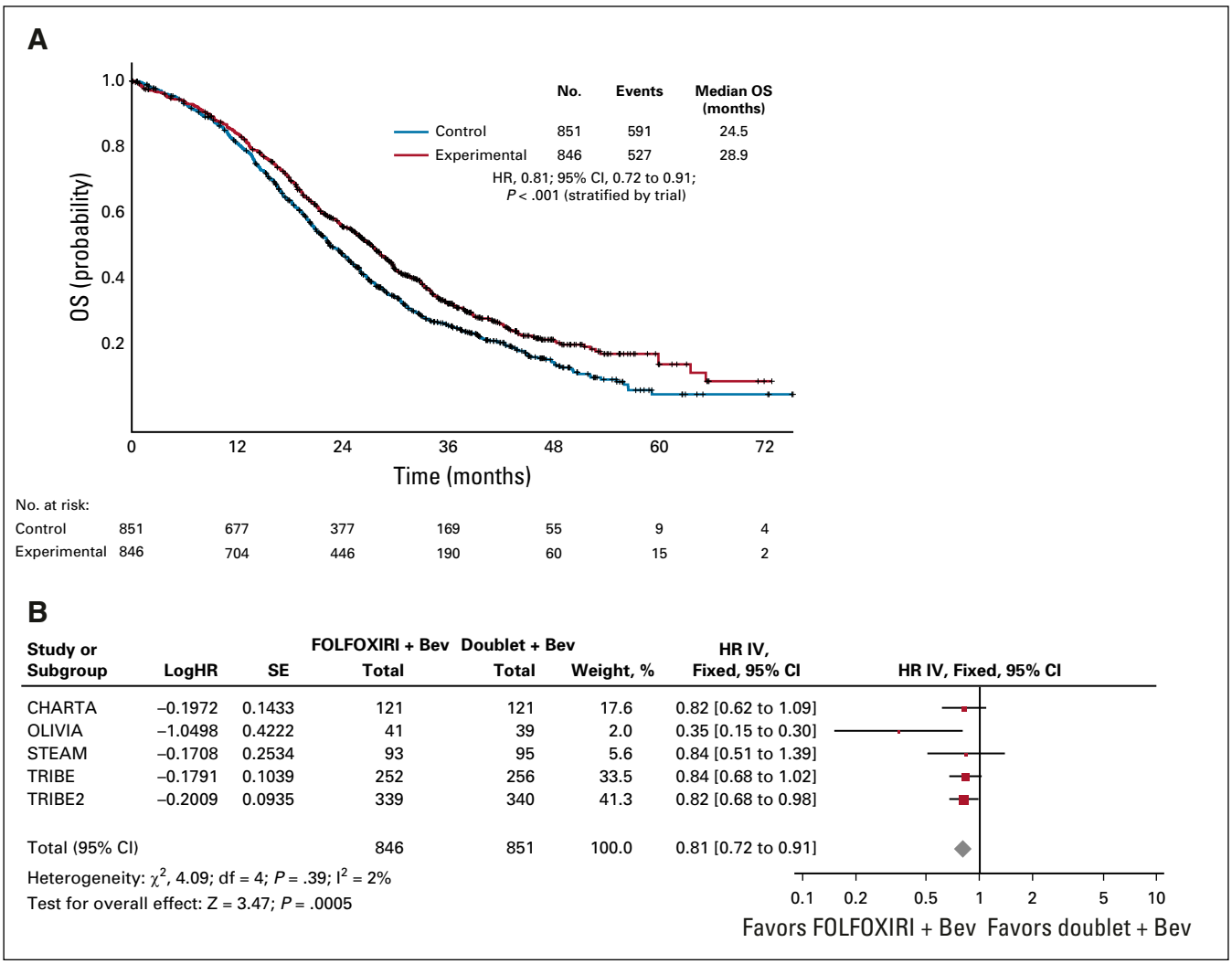

FIG 1. (A) Overall survival (OS) curves by treatment arm. (B) Forest plot of treatment effect on OS. Bev, bevacizumab; FOLFOXIRI, infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan; HR, hazard ratio; IV, inverse variance.

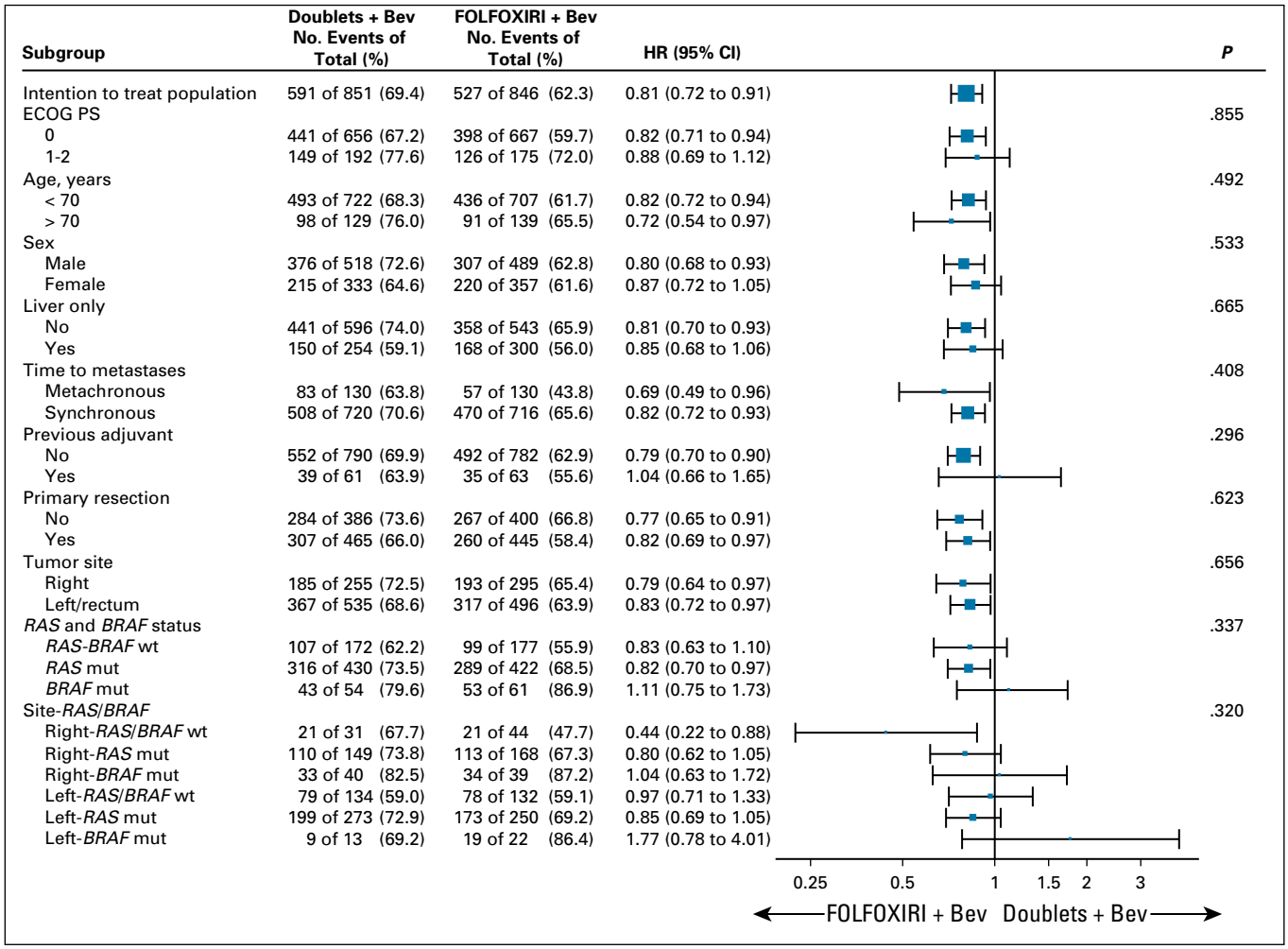

FIG 2. Treatment effect on overall survival within main clinical and molecular subgroups. Bev, bevacizumab; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFOXIRI, infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan; HR, hazard ratio; mut, mutation; wt, wild type.

(hazard ratio [HR], 0.81; 95% CI, 0.72 to 0.91; $P < .001$; Fig 1A). The estimated 5-year OS rate was 22.3% (95% CI, 18.0% to 26.6%) in the FOLFOXIRI + bevacizumab group and 10.7% (95% CI, 6.6% to 14.8%) in the doublets + bevacizumab group ($P < .001$). No significant heterogeneity among the 5 trials ($P = .39$; $I^2 = 2\%$; Fig 1B) was detected. Treatment effect was consistent across analyzed subgroups (Fig 2). Although in the absence of a significant P for interaction ($P = .104$), patients previously exposed to an oxaliplatin-based adjuvant therapy derived no benefit from FOLFOXIRI + bevacizumab versus doublets + bevacizumab (Data Supplement). OS results in the *BRAF*-mutant subgroup and according to the comparator arm (oxaliplatin *v* irinotecan based) are described in the Data Supplement.

A total of 1,489 (88%) patients experienced first-line disease progression (761 [89%] in the doublets + bevacizumab group and 728 [86%] in the FOLFOXIRI + bevacizumab group). Median PFS was 12.2 months (95% CI, 11.6 to 12.8 months) in the FOLFOXIRI + bevacizumab group and 9.9 months (95% CI, 9.5 to 10.3 months) in the doublets + bevacizumab group (HR, 0.74; 95% CI, 0.67 to 0.82; $P < .001$; Fig 3A). No significant heterogeneity among the 5 trials was observed ($P = .19$; $I^2 = 35\%$; Fig 3B). Treatment effect was consistent across analyzed subgroups (Data Supplement). A borderline significant interaction ($P = .058$) was found between treatment effect and the previous exposure to an oxaliplatin-based adjuvant therapy (Data Supplement)

Among 1,695 (99.9%) of the 1,697 patients evaluable for RECIST, 545 (64.5%) of 845 in the FOLFOXIRI + bevacizumab group and 456 (53.6%) of 850 in the doublets + bevacizumab group achieved an objective response (odds ratio [OR], 1.57; 95% CI, 1.29 to 1.91; $P < .001$). There was no evidence of heterogeneity among the 5 trials ($P = 1.00$; $I^2 = 0\%$; Data Supplement) or among investigated subgroups (Data Supplement).

Secondary surgery for metastases was performed with a radical curative intent (ie, R0 resection) for 139 patients (16.4%) in the FOLFOXIRI + bevacizumab group and 100

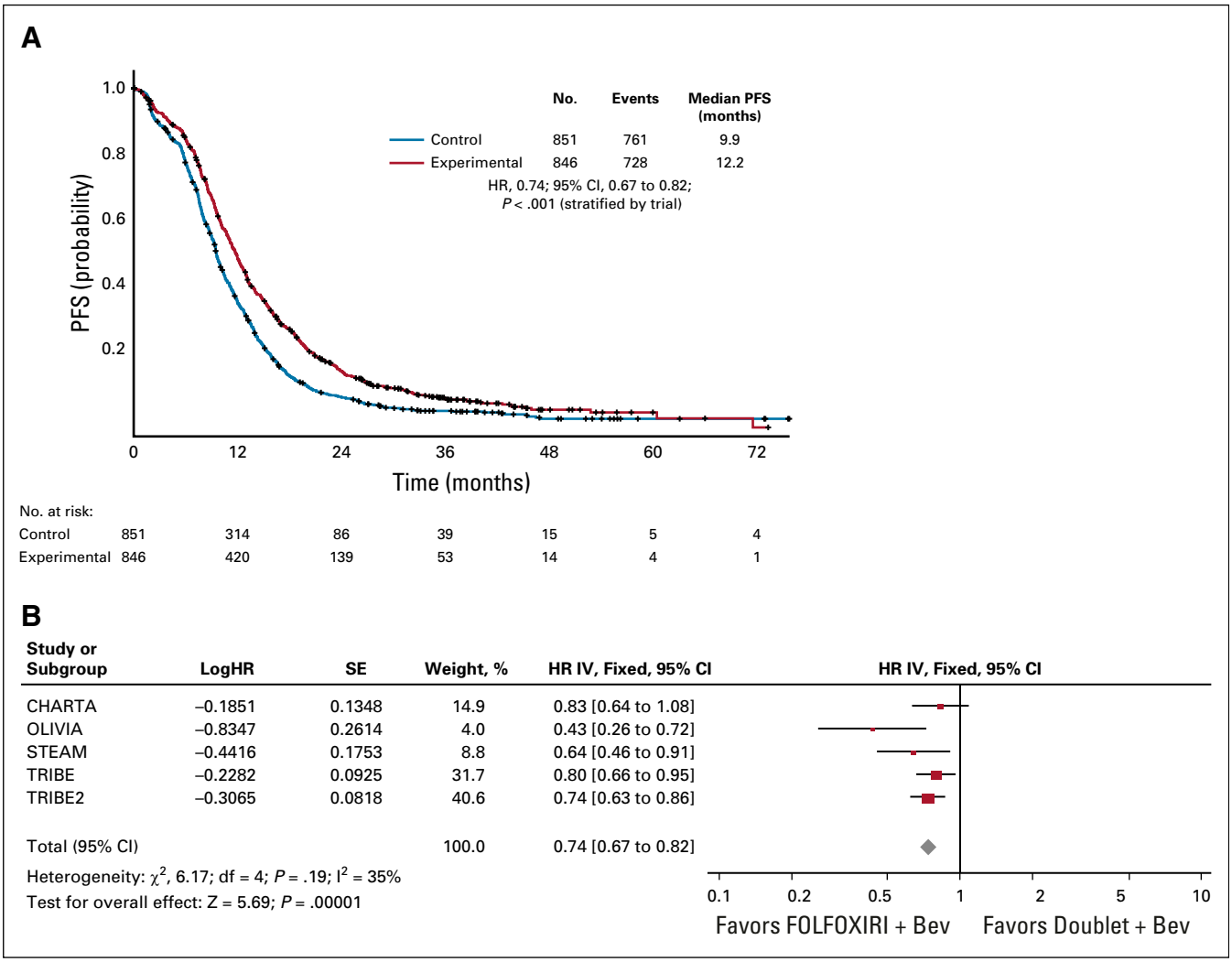

FIG 3. (A) Progression-free survival (PFS) curves by treatment arm. (B) Forest plot of treatment effect on PFS. Bev, bevacizumab; FOLFOXIRI, infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan; HR, hazard ratio; IV, inverse variance.

patients (11.8%) in the doublets + bevacizumab group (OR, 1.48; 95% CI, 1.12 to 1.95; $P = .007$; Data Supplement). No evidence of heterogeneity among the 5 trials was observed ($P = .33$; $I^2 = 13\%$).

A sensitivity analysis explored the survival difference between treatment arms in patients who underwent R0 resection or not following the upfront therapy. There was no significant interaction between treatment arm and the achievement of R0 resection in terms of OS ($P = .667$). In patients with R0 resection, median OS was 64.0 months with FOLFOXIRI + bevacizumab and 52.6 months with doublets + bevacizumab (HR, 0.79; 95% CI, 0.50 to 1.24), while in other patients, median OS was 25.7 and 22.3 months, respectively (HR, 0.84; 95% CI, 0.74 to 0.95; Data Supplement).

Of the 1,697 patients, 1,674 (98.6%) were included in the safety analysis (23 patients did not receive any dose of the assigned treatment and were excluded [15 in the doublets + bevacizumab arm and 8 in the FOLFOXIRI + bevacizumab arm]). Compared with doublets + bevacizumab, the administration of FOLFOXIRI + bevacizumab was associated with a significantly higher incidence of the following grade 3 or 4 adverse events: neutropenia (45.8% *v* 21.5%; $P < .001$), febrile neutropenia (6.3% *v* 3.7%; $P = .019$), nausea (5.5% *v* 3.0%; $P = .016$), mucositis (5.1% *v* 2.9%; $P = .024$), and diarrhea (17.8% *v* 8.4%; $P < .001$). No significant increase in the rate of toxic deaths was reported (2.3% *v* 1.4%; $P = .277$; Fig 4).

DISCUSSION

The present meta-analysis of IPD from 5 randomized trials provides robust confirmation of the survival benefit from FOLFOXIRI + bevacizumab compared with doublets + bevacizumab as initial therapy of unresectable mCRC. The advantage with FOLFOXIRI + bevacizumab is not only statistically significant but also clinically meaningful: A reduction in the risk of death of 19% is reported, with a 4.

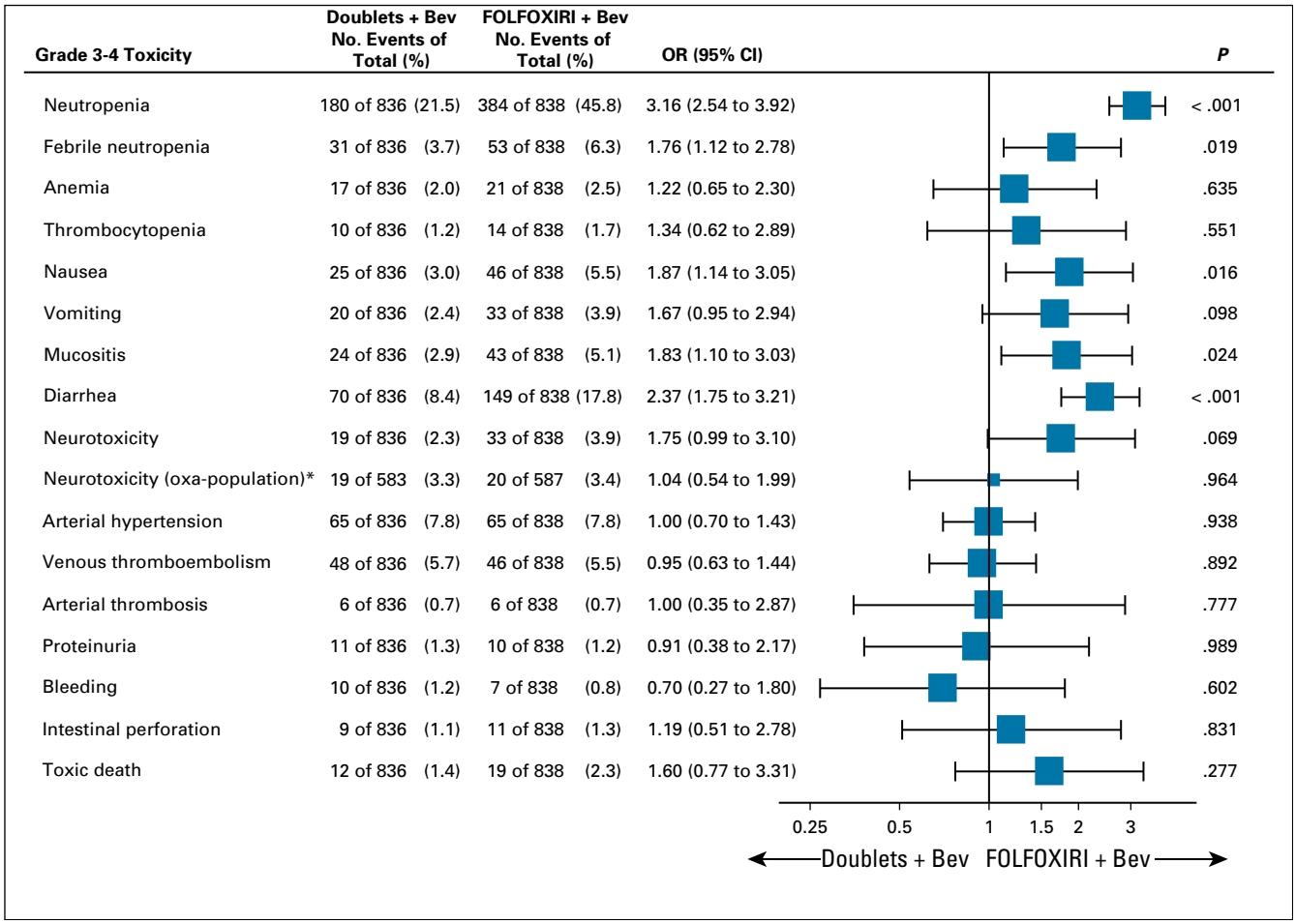

FIG 4. Odds ratios (ORs) of most frequent grade 3 or 4 adverse events. (*) Excludes patients in the TRIBE study. Bev, bevacizumab; FOLFOXIRI, infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan; oxa, oxaliplatin.

4-month absolute difference in median OS and, notably, an 11.6% relative increase in the estimated 5-year OS rate that reaches 22.3% with FOLFOXIRI + bevacizumab. The consistent benefit observed in terms of PFS, ORR, and radical resections corroborates OS results. Therefore, our findings provide a reliable answer to one of the most frequently reported concerns with regard to the upfront use of the 3 cytotoxics: the short-term effect of the intensified regimen not followed by a coherent long-term benefit. The current results should be reassuring about the worry that the exposure to the 3 drugs may impair the efficacy of subsequent therapies, thus not translating into a relevant survival advantage. Results of another randomized study that compared FOLFOXIRI + bevacizumab and FOLFOX + bevacizumab as upfront treatment of poor-prognosis mCRC with at least 3 circulating tumor cells detected at baseline were recently presented and are consistent with findings from our meta-analysis.[11]

With the aim of improving the estimation of the cost/benefit balance of the upfront use of FOLFOXIRI + bevacizumab, the price of the intensified chemotherapy in terms of toxicity cannot be neglected. Higher incidence of grade 3 and 4 GI (diarrhea, mucositis, nausea) and hematologic (neutropenia, febrile neutropenia) adverse events was confirmed, with no increase in bevacizumab-related toxicities or fatal events. The overall incidence of febrile neutropenia was 6%, thus below the threshold for recommending the routine use of granulocyte colony-stimulating factor as primary prophylaxis.[17] Of note, results are consistent among different trials conducted in different geographic areas. Quality-of-life data are missing for most of the trials, though. However, in the CHARTA study, no impairment of quality of life as assessed by means of the EORTC QLQ C30 (global health score) was reported in the FOLFOXIRI + bevacizumab group.

To minimize the impact of toxicity and maximize treatment efficacy, an appropriate selection of candidate patients is mandatory. Even if the enrollment of patients with ECOG performance status 2 was allowed in the TRIBE, TRIBE2, and CHARTA studies, the 99% of patients included in the current meta-analysis had an ECOG performance status of 0 or 1, and the median age was 61 years. In the TRIBE, TRIBE2, and STEAM trials, patients age > 75 years were not eligible, and for those between 70 and 75 years of age,

an ECOG performance status of 0 was required. The same criteria should be adopted in daily practice. A pooled analysis of the TRIBE and TRIBE2 studies also showed higher rates of grade 3 and 4 diarrhea and neutropenia among patients > 70 years old, thus underlining that the higher efficacy of the triplet should be carefully balanced with the higher risk of clinically relevant toxicities in this subgroup.[18] In this regard, the CHARTA study defined no age limit for eligibility, but elderly and frail patients received a first cycle of therapy at a reduced dose, and then doses were adapted based on toxicity.

Identifying disease characteristics associated with higher benefit from the intensification of the upfront chemotherapy would be helpful to draw the portrait of the ideal candidate for FOLFOXIRI + bevacizumab. Nevertheless, among investigated subgroups, no characteristics associated with higher benefit from the intensified regimen were identified. However, as previously shown in the TRIBE study, patients exposed to an oxaliplatin-based adjuvant therapy seemed not to derive benefit from FOLFOXIRI + bevacizumab compared with doublets + bevacizumab.

Overall, only a minority (20%) of patients included had a left-sided *RAS* and *BRAF* wild-type tumor as a consequence of the increased use of anti-EGFR antibodies in first-line therapy in past years, so the combination of a chemotherapy doublet with an anti-EGFR remains a preferred option in these patients.[1-3] Studies that investigated the added value of the intensified chemotherapy in combination with anti-EGFRs are currently ongoing: ClinicalTrials.gov identifiers: NCT03493048 and NCT01802645.[19,20]

In past years, the use of FOLFOXIRI + bevacizumab has been often considered the preferable option in *BRAF* V600E–mutated tumors with the aim of rapidly counteracting the biologic aggressiveness of these poor-prognosis tumors.[1,3] This recommendation was based on the subgroup analysis of the phase III TRIBE study showing a higher magnitude of benefit from FOLFOXIRI + bevacizumab compared with FOLFIRI + bevacizumab in the *BRAF*-mutated subgroup, although in the absence of a significant interaction effect between treatment arm and *RAS* or *BRAF* mutational status.[7] These results corroborated previous findings from a prospective phase II study of FOLFOXIRI + bevacizumab in patients with *BRAF* V600E–mutated mCRC, which provided encouraging signals of activity.[21] However, results of the TRIBE2 study did not confirm the suggestion of the previous TRIBE study,[12] and the present meta-analysis further challenges the role of FOLFOXIRI + bevacizumab in *BRAF*-mutated tumors because no increased benefit from the intensified approach is evident in this subgroup. The different comparator arm (FOLFIRI + bevacizumab in the TRIBE study *v* FOLFOX + bevacizumab in all the other trials) may explain these results. However, the use of FOLFOXIRI + bevacizumab should no longer be regarded as the first choice for patients with *BRAF*-mutant tumors, where the use of FOLFOX + bevacizumab seems the preferable upfront option.

Another decision driver for the choice of the first-line therapy is the treatment aim: In patients with the potential for resection, an active upfront treatment allows for not missing the opportunity to convert the disease to resectability.[1-3] Consistently, FOLFOXIRI + bevacizumab is often considered a valuable choice when the secondary resection of metastases is a pursuable treatment objective, mainly in the case of liver-limited spread.[22,23] However, most of patients included in the present meta-analysis were not selected based on the extent of metastatic spread and/or potential conversion to resectability. In an exploratory sensitivity analysis, no interaction effect was found between treatment arm and the achievement of R0 resections, thus confirming that the benefit from FOLFOXIRI + bevacizumab is not limited to patients who undergo radical resection of their lesions and indirectly demonstrates that the survival benefit reported with FOLFOXIRI + bevacizumab is not only due to the higher rate of patients converted to R0 resection.

In conclusion, on the basis of the results of our meta-analysis, FOLFOXIRI + bevacizumab is a valuable upfront option able to provide a clinically meaningful survival benefit to patients with unresectable mCRC with an ECOG performance status of 0 or 1. Assessment of the value of the addition of bevacizumab to FOLFOXIRI or the comparative efficacy versus doublets plus anti-EGFR in patients with *RAS* wild-type tumors is out of the reach of the current work. Younger patients with right-sided and/or *RAS*-mutated tumors not exposed to a previous oxaliplatin-based adjuvant regimen may be the best candidates for this approach independently of the conversion intent. The personalized estimation of the cost/benefit balance of chemotherapy intensification should take into account patient-related characteristics, including personal beliefs, attitudes, and expectations.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Individual Patient Data Meta-Analysis of FOLFOXIRI Plus Bevacizumab Versus Doublets Plus Bevacizumab as Initial Therapy of Unresectable Metastatic Colorectal Cancer

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