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ORIGINAL ARTICLE

Primary tumor sidedness and benefit from FOLFOXIRI plus bevacizumab as initial therapy for metastatic colorectal cancer. Retrospective analysis of the TRIBE trial by GONO

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Background: Right-sided metastatic colorectal cancer (mCRC) patients have poor prognosis and achieve limited benefit from first-line doublets plus a targeted agent. In this unplanned analysis of the TRIBE study, we investigated the prognostic and predictive impact of primary tumor sidedness in mCRC patients and the differential impact of the intensification of the chemotherapy in subgroups defined according to both primary tumor sidedness and *RAS* and *BRAF* mutational status.

Patients and methods: Patients were randomized to receive upfront 5-fluoruracil, leucovorin, and irinotecan (FOLFIRI) plus bevacizumab or 5-fluoruracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) plus bevacizumab. Tumors were defined as right- or left-sided if they originated from the caecum to the transverse colon or within the splenic flexure and beyond, respectively. Patients with available information about both primary sidedness and *RAS* and *BRAF* status were included in the present analysis. Progression-free survival (PFS), overall survival (OS) and RECIST response rate were assessed according to tumor location and *RAS* and *BRAF* mutational status.

Results: Information about primary sidedness and *RAS* and *BRAF* status was available for 358 (70.5%) out of 508 randomized patients. Patients with right-sided tumors ($N = 173$) presented shorter OS [23.7 versus 31.0 months, HR = 1.42 (95% CI 1.09–1.84), $P = 0.010$] and a trend toward shorter PFS [10.2 versus 11.5 months, HR = 1.24 (95% CI: 0.98–1.56), $P = 0.083$] than those with left-sided tumors ($N = 185$), but these associations were no longer evident when adjusting for *RAS* and *BRAF* status. Patients with right-sided tumors achieved more relative benefit from the intensification of the chemotherapy backbone in terms of both PFS (HR = 0.59 versus 0.89, P for interaction = 0.099) and OS (HR = 0.56 versus 0.99, P for interaction = 0.030) and this advantage was independent of their *RAS* and *BRAF* status.

Conclusions: FOLFOXIRI plus bevacizumab may be regarded as a preferred first-line treatment option for clinically selected patients with right-sided metastatic colorectal cancer irrespective of their *RAS* and *BRAF* mutational status. Trial registration: clinicaltrials.gov identifier NCT00719797.

Key words: metastatic colorectal cancer, primary sidedness, FOLFOXIRI plus bevacizumab, RAS and BRAF mutational status

Introduction

Recent evidence from clinical trials and translational studies highlights that biologic, molecular and immunologic differences between right- and left-sided colorectal cancers translate into significant clinical differences, with relevant implications in metastatic patients' management [1–5].

A wide amount of data consistently shows that left-sidedness is associated with better prognosis [6] and meaningful benefit from anti-EGFR agents [7], thus leading to consider EGFR blockade as a preferred upfront strategy for *RAS* and *BRAF* wild-type patients [8, 9]. On the other hand, right-sidedness predicts poor prognosis and resistance to anti-EGFRs also in *RAS* and *BRAF* wild-type tumors [8, 9], thus pointing out the contribution of molecular or environmental factors other than *BRAF* mutation to these findings. Limited survival results are achieved in these patients with first-line doublets plus a biologic agent, thus highlighting the need to investigate how to counteract the intrinsic aggressiveness of right-sided tumors [8, 9].

The academic phase III TRIBE trial reported significant progression-free survival (PFS) and OS benefit from the addition of oxaliplatin to FOLFIRI plus bevacizumab in previously untreated metastatic colorectal cancer (mCRC) patients [10, 11].

In this unplanned subgroup analysis of the TRIBE study we investigated whether the effect of the intensification of the upfront chemotherapy backbone was different according to tumor sidedness, and whether this potentially heterogeneous effect differed according to *RAS* and *BRAF* mutational status.

Methods

Study design and patients

The TRIBE design, treatments, eligibility and exclusion criteria, and study procedures have been previously reported [11]. PFS was the primary end point. The study was approved by Ethics Committees at each participating center and was conducted in accordance with the Declaration of Helsinki. All patients provided their written informed consent. Only patients with available information about both primary sidedness and *RAS* and *BRAF* mutational status are included in the present analysis.

Definition of primary sidedness

Coherently with previous subgroup analyses of other randomized studies, tumors located in the caecum, ascending and transverse colon were defined as right-sided, while those located within the splenic flexure and beyond were defined as left-sided.

Definition of end points

PFS was defined as the time from randomization to the evidence of disease progression according to RECIST version 1.1, or death, whichever

Table 1. Demographic and baseline characteristics of study population according to primary tumor sidedness and treatment arm

Characteristics	Right-sided tumors (*N* = 116)		Left-sided tumors (*N* = 242)	
	FOLFIRI plus bev (*N* = 44)	FOLFOXIRI plus bev (*N* = 72)	FOLFIRI plus bev (*N* = 129)	FOLFOXIRI plus bev (*N* = 113)
Age				
Median	61	61	59	59
Range	29–74	31–75	38–75	29–75
Gender, *N* (%)				
Male	31 (71)	45 (63)	67 (52)	75 (66)
Female	13 (29)	27 (37)	62 (48)	38 (34)
ECOG PS, *N* (%)				
0	38 (86)	63 (88)	116 (90)	101 (89)
1–2	6 (14)	9 (12)	13 (10)	12 (11)
Previous adjuvant therapy, *N* (%)				
No	40 (91)	64 (89)	110 (85)	99 (88)
Yes	4 (9)	8 (11)	19 (15)	14 (12)
Time to metastases, *N* (%)				
Synchronous	38 (86)	58 (81)	101 (78)	90 (80)
Metachronous	6 (14)	14 (19)	28 (22)	23 (20)
Sites of metastases, *N* (%)				
Single	7 (16)	25 (35)	34 (26)	35 (31)
Multiple	37 (84)	47 (65)	95 (74)	78 (69)
RAS/*BRAF* status, *N* (%)				
RAS and *BRAF* wild-type	9 (20)	16 (22)	52 (40)	47 (42)
RAS mutated	28 (64)	48 (67)	73 (57)	60 (53)
BRAF mutated	7 (16)	8 (11)	4 (3)	6 (5)

ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan; bev, bevacizumab.

Table 2. Efficacy and activity results in subgroups defined according to primary tumor sidedness and RAS and BRAF mutational status

	Study population				*RAS* and *BRAF* wild-type				*RAS* mutant				*BRAF* mutant			
	Right-sided (*N* = 116)		Left-sided (*N* = 242)		Right-sided (*N* = 25)		Left-sided (*N* = 99)		Right-sided (*N* = 76)		Left-sided (*N* = 133)		Right-sided (*N* = 15)		Left-sided (*N* = 10)	
PFS																
Median (mos)	10.2		11.5		12.3		12.2		10.1		11.5		6.7		7.0	
HR [95% CI]	1.24 [0.98–1.56]				1.40 [0.89–2.20]				1.08 [0.80–1.46]				1.02 [0.45–2.28]			
P	0.083				0.616[a]											
OS																
Median (mos)	23.7		31.0		25.8		38.0		24.5		26.2		10.2		13.4	
HR [95% CI]	1.42 [1.09–1.84]				1.72 [1.03–2.85]				1.19 [0.85–1.65]				1.17 [0.50–2.75]			
P	0.010				0.478[a]											
ORR																
Rate, %	60.3		60.3		76.0		64.7		59.2		57.1		40.0		60.0	
OR [95% CI]	0.98 [0.61–1.57]				1.57 [0.57–4.37]				0.99 [0.55–1.79]				0.65 [0.12–3.56]			
P	0.937				0.622[a]											
	FOLFOXIRI +bev *N*=72	**FOLFIRI +bev *N*=44**	**FOLFOXIRI +bev *N*=113**	**FOLFIRI +bev *N*=129**	**FOLFOXIRI +bev *N*=16**	**FOLFIRI +bev *N*=9**	**FOLFOXIRI +bev *N*=47**	**FOLFIRI +bev *N*=52**	**FOLFOXIRI +bev *N*=48**	**FOLFIRI +bev *N*=28**	**FOLFOXIRI +bev *N*=60**	**FOLFIRI +bev *N*=73**	**FOLFOXIRI +bev *N*=8**	**FOLFIRI +bev *N*=7**	**FOLFOXIRI +bev *N*=6**	**FOLFIRI +bev *N*=4**
PFS																
Median (mos)	11.2	9.4	10.7	11.0	13.4	10.1	14.1	11.5	11.0	9.6	12.5	9.6	9.0	4.2	6.5	10.9
HR [95% CI]	0.59 [0.40–0.88]		0.89 [0.68–1.16]		0.54 [0.24–1.22]		0.85 [0.56–1.29]		0.67 [0.41–1.10]		0.88 [0.61–1.26]		0.33 [0.12–0.92]		1.74 [0.48–6.30]	
P	0.099[a]				0.292[a]											
OS																
Median (mos)	26.0	20.2	28.6	31.6	31.5	22.3	40.0	37.7	26.3	20.5	27.2	25.6	20.4	9.4	12.0	25.2
HR [95% CI]	0.56 [0.37–0.85]		0.99 [0.73–1.35]		0.50 [0.21–1.02]		0.88 [0.54–1.44]		0.67 [0.40–1.14]		1.02 [0.68–1.52]		0.22 [0.07–0.67]		2.02 [0.50–8.15]	
P	0.030[a]				0.165[a]											
ORR																
Rate, %	63.9	54.6	64.6	56.6	81.3	66.7	63.8	65.4	62.5	53.6	65.0	50.7	37.5	42.9	66.7	50.0
OR [95% CI]	1.48 [0.68–3.26]		1.43 [0.84–2.44]		2.17 [0.33–14.06]		0.93 [0.41–2.13]		1.44 [0.56–3.72]		1.81 [0.90–3.64]		0.80 [0.10–6.35]		2.00 [0.15–26.73]	
P	0.942[a]				0.584[a]											

All the analyses are adjusted for ECOG PS (0 versus 1–2) and previous exposure to adjuvant therapy (yes versus no).

[a]*P* for interaction.

FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan; bev, bevacizumab; mos, months; HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; OR, odds ratio.

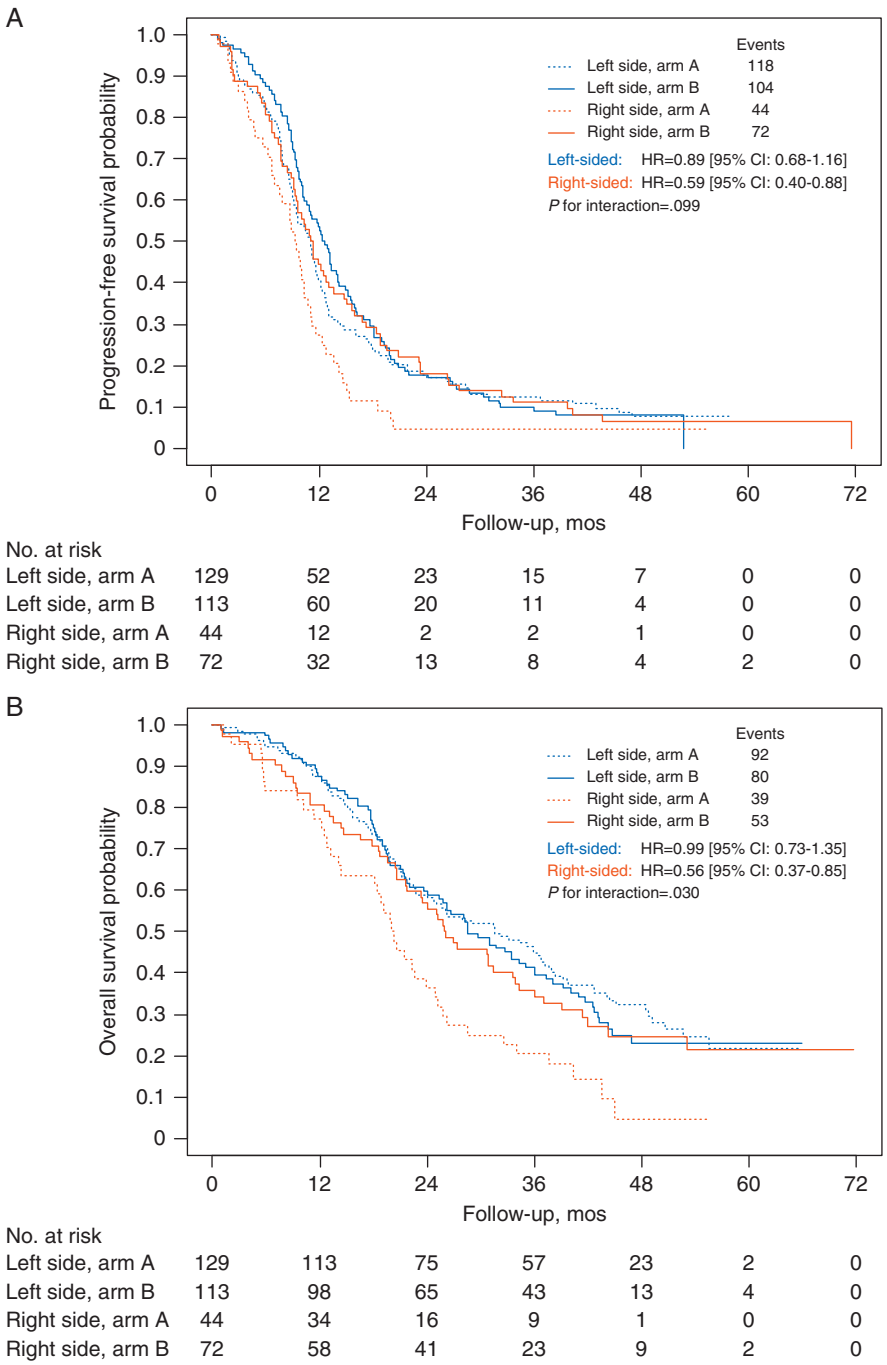

Figure 1. Kaplan–Meier estimates of PFS and OS according to primary sidedness and treatment arm. (A) Progression-free survival and (B) overall survival. HR, hazard ratio; mos, months; Arm A indicates FOLFIRI plus bevacizumab. Arm B indicates FOLFOXIRI plus bevacizumab.

occurred first; overall survival (OS) was defined as the time from randomization to death from any cause; overall response rate (ORR) was defined as the proportion of patients achieving partial or complete response according to RECIST version 1.1.

Statistical analysis

Survival functions from time-to-event data were estimated with the Kaplan–Meier product limit method. The association between primary sidedness and molecular status with survival parameters and ORR was assessed with Cox and logistic regression models, respectively, including ECOG PS, previous adjuvant chemotherapy and treatment arm as covariates. Subgroup analyses were done including an interaction term in the statistical models.

Results

Study population and baseline characteristics

Information about primary sidedness and *RAS* and *BRAF* mutational status were available for 358 (70%) out of 508 patients

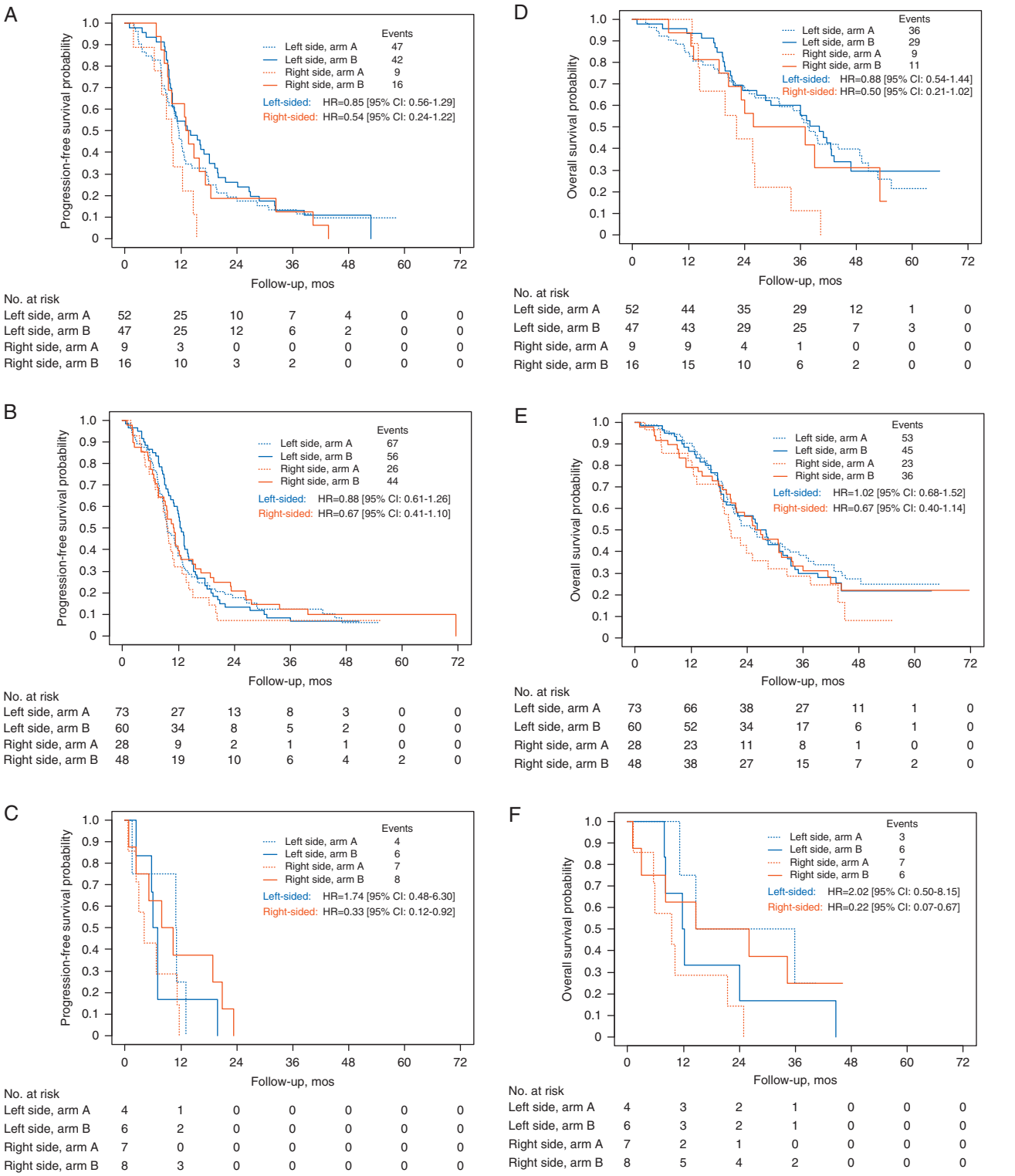

Figure 2. Kaplan–Meier estimates of PFS and OS according to *RAS* and *BRAF* mutational status, primary sidedness and treatment arm. (A) Progression-free survival in *RAS* and *BRAF* wild-type tumors. (B) Progression-free survival in *RAS* mutant tumors. (C) Progression-free survival in *BRAF* mutant tumors. (D) Overall survival in *RAS* and *BRAF* wild-type tumors. (E) Overall survival in *RAS* mutant tumors. (F) Overall survival in *BRAF* mutant tumors. HR, hazard ratio; Arm A indicates FOLFIRI plus bevacizumab. Arm B indicates FOLFOXIRI plus bevacizumab.

randomized in the TRIBE trial. One hundred and seventy-three (48%) and 185 (52%) patients had right- and left-sided primary tumors, respectively. Their distribution between treatment arms was unbalanced, since a higher percentage of patients with right-sided tumors were allocated to arm B than to arm A (39% versus 25%, $P = 0.006$). Baseline characteristics according to primary sidedness and treatment arm are summarized in Table 1.

One hundred and twenty-four (35%), 209 (58%) and 25 (7%) patients had *RAS* and *BRAF* wild-type, *RAS* mutated or *BRAF* mutated tumors, respectively, with no imbalances between treatment arms ($P = 0.894$). As compared with left-sided tumors, right-sided ones harbored more frequently *RAS* (66% versus 55%) and *BRAF* mutations (13% versus 4%) ($P < 0.001$).

As compared with patients with left-sided primary tumors, those with right-sided tumors presented shorter OS [23.7 months versus 31.0 months, HR, 1.42 (95% CI 1.09–1.84), $P = 0.010$] and a trend toward shorter PFS [10.2 months versus 11.5 months, HR, 1.24 (95% CI 0.98–1.56), $P = 0.083$]. When adjusting for mutational status, the impact of primary sidedness on PFS was not significant [HR, 1.15 (95% CI 0.90–1.47, $P = 0.252$)], while a trend was retained in terms of OS [HR, 1.30 (95% CI 0.99–1.70), $P = 0.061$]. No difference was evident in ORR ($P = 0.937$). The prognostic effect of primary sidedness across different molecular subgroups is described in Table 2.

Primary tumor sidedness was associated with differential treatment effect in terms of PFS (P for interaction = 0.099) and OS (P for interaction = 0 .030), with higher benefit from the intensification of the chemotherapy backbone among patients with right- than left-sided tumors (Table 2 and Figure 1), while no differences were evident in ORR (P for interaction = 0.942).

When looking at the predictive impact of primary sidedness according to *RAS* and *BRAF* status, no significant interaction was reported either in terms of PFS ($P = 0.292$), OS ($P = 0.165$) or ORR ($P = 0.584$). However, a differential treatment effect favoring right-sided tumors was evident in PFS and OS in all molecular subgroups (Table 2 and Figure 2).

Results about the prognostic and predictive role of *RAS* and *BRAF* mutational status are summarized in supplementary Table S1, available at *Annals of Oncology* online.

Discussion

The recent interest in primary sidedness as a potential driver of treatment choices was raised by post hoc analyses of head-to-head trials of first-line doublets plus either bevacizumab or an anti-EGFR [8, 9]. Consistent results were provided in the *RAS* wild-type subgroups of FIRE-3 [12], CALGB80405 [13] and PEAK [14] studies strengthening the clear association of right-sidedness with poor prognosis but also highlighting a new role for primary sidedness as a predictor of benefit from anti-EGFRs.

Overall, while available data clearly identify doublets plus an anti-EGFR as a preferred option for left-sided tumors, it remained unclear how to improve poor survival results achieved in right-sided primaries with doublets plus a biologic [8, 9].

Here we show that the relative benefit from FOLFOXIRI plus bevacizumab over FOLFIRI plus bevacizumab is much more pronounced in right-sided tumors independently of their *RAS* and *BRAF* status. Though acknowledging the limited power of our analysis, the relative over-representation of *RAS* mutant patients in this study and the limited number of *BRAF* mutants, in all molecular subgroups treatment effect is heterogeneous among right- and left-sided tumors. Moreover, though recognizing methodological limitations of cross-trial comparisons, the triplet plus bevacizumab in molecularly unselected patients allowed achieving remarkably better survival results than doublets plus a biologic in the *RAS* wild-type subgroup of other contemporary trials in right-sided tumors [10].

As a consequence, based on present findings, FOLFOXIRI plus bevacizumab may be regarded as a preferred option for patients with right-sided tumors, fit for combination, meeting clinical criteria for the use of the triplet (i.e. age 18–75 years; ECOG PS 0–2 if age ≤70 years, or 0 if age 71–75 years) [15], independently of their molecular status. On the other side, in left-sided tumors, the benefit from the intensification of the chemotherapy backbone appears less pronounced, thus leading to consider doublets plus an anti-EGFR as a preferred option in *RAS* and *BRAF* wild-type patients, In order to validate present exploratory results, an individual-patient data metanalysis of randomized trials comparing triplet plus bevacizumab versus doublets plus bevacizumab is currently ongoing.

Conclusion

According to this unplanned subgroup analysis of the TRIBE study, FOLFOXIRI plus bevacizumab may be able to efficiently counteract the intrinsic aggressiveness of right-sided mCRCs.

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Disclosures

CC is a consultant/advisory board member for Roche, Amgen, Eli-Lilly, Bayer, Merck Serono. GT has received personal fees from Novartis, F Hofi man-La Roche and Molteni. GM has received personal fees from Amgen, F Hofiman-La Roche, Bayer, Merk Serono and Sirtex. AF is a consultant/advisory board member for Bayer, Roche, Amgen, Eli-Lilly, Merck Serono, Sanofi, Servier. All remaining authors have declared no conflicts of interest.

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