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ORIGINAL ARTICLE

Biomarker analysis beyond angiogenesis: *RAS/RAF* mutation status, tumour sidedness, and second-line ramucirumab efficacy in patients with metastatic colorectal carcinoma from RAISE—a global phase III study

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Background: : Second-line treatment with ramucirumab+FOLFIRI improved overall survival (OS) versus placebo+FOLFIRI for patients with metastatic colorectal carcinoma (CRC) [hazard ratio (HR)=0.84, 95% CI 0.73–0.98, $P = 0.022$]. Post hoc analyses of RAISE patient data examined the association of *RAS/RAF* mutation status and the anatomical location of the primary CRC tumour (left versus right) with efficacy parameters.

Patients and methods: Patient tumour tissue was classified as *BRAF* mutant, *KRAS/NRAS* (*RAS*) mutant, or *RAS/BRAF* wild-type. Left-CRC was defined as the splenic flexure, descending and sigmoid colon, and rectum; right-CRC included transverse, ascending colon, and cecum.

Results: *RAS/RAF* mutation status was available for 85% of patients (912/1072) and primary tumour location was known for 94.4% of patients (1012/1072). A favourable and comparable ramucirumab treatment effect was observed for patients with *RAS* mutations (OS HR = 0.86, 95% CI 0.71–1.04) and patients with *RAS/BRAF* wild-type tumours (OS HR = 0.86, 95% CI 0.64–1.14). Among the 41 patients with *BRAF*-mutated tumours, the ramucirumab benefit was more notable (OS HR = 0.54, 95% CI 0.25–1.13), although, as with the other genetic sub-group analyses, differences were not statistically significant. Progression-free survival (PFS) data followed the same trend. Treatment-by-mutation status interaction tests (OS $P = 0.523$, PFS $P = 0.655$) indicated that the ramucirumab benefit was not statistically different among the mutation sub-groups, although the small sample size of the *BRAF* group limited the analysis. Addition of ramucirumab to FOLFIRI improved left-CRC median OS by 2.5 month over placebo (HR = 0.81, 95% CI 0.68–0.97); median OS for ramucirumab-treated patients with right-CRC was

1.1 month over placebo (HR = 0.97, 95% CI 0.75–1.26). The treatment-by-sub-group interaction was not statistically significant for tumour sidedness ($P = 0.276$).

Conclusions: In the RAISE study, the addition of ramucirumab to FOLFIRI improved patient outcomes, regardless of *RAS/RAF* mutation status, and tumour sidedness. Ramucirumab treatment provided a numerically substantial benefit in *BRAF*-mutated tumours, although the *P*-values were not statistically significant.

ClinicalTrials.gov number: NCT01183780.

Key words: colorectal carcinoma, ramucirumab, BRAF, KRAS, NRAS, left

Introduction

The global, randomised, double-blind, placebo-controlled, RAISE phase III trial examined whether patients with metastatic colorectal carcinoma (mCRC) who had been previously treated with first-line bevacizumab, oxaliplatin, and a fluoropyrimidine would exhibit improved survival when ramucirumab was added to second-line FOLFIRI (folinic acid, 5-fluorouracil, and irinotecan) treatment [1]. The human IgG1 monoclonal antibody, ramucirumab, inhibits tumour angiogenesis by binding to vascular endothelial growth factor (VEGF) receptor-2 (VEGFR-2) and interfering with VEGF ligand binding [2]. Results from the RAISE trial indicated that the addition of ramucirumab to second-line FOLFIRI improved overall survival (OS) over placebo+FOLFIRI [median OS 13.3 versus 11.7 months; hazard ratio (HR)=0.84; 95% confidence interval (CI) 0.73–0.98; $P = 0.022$) [1]. Median progression-free survival (PFS) was also extended by the addition of ramucirumab (5.7 versus 4.5 months, HR = 0.79; 95% CI 0.70–0.90; $P < 0.0005$) [1].

Analysis of patient sub-groups and biomarkers has aimed to identify patient or tumour characteristics associated with an improved ramucirumab benefit. Using an exploratory assay, high baseline plasma VEGF-D levels (≥115 pg/ml) were associated with better survival outcomes for ramucirumab-treated patients [3]. Low baseline plasma carcinoembryonic antigen (CEA) levels (≤10 ng/ml) were also associated with an enhanced ramucirumab response [4]. The *KRAS* exon 2 mutation is known to affect CRC response to EGFR inhibitors, but its impact, if any, on ramucirumab is not known. A pre-specified analysis showed that both *KRAS* exon 2 mutant and *KRAS* exon 2 wild-type tumours demonstrated a consistent survival benefit in favour of the ramucirumab+FOLFIRI arm [5]. More recent data demonstrated that other *RAS* mutations (*KRAS* exons 3 and 4, *NRAS*) and the *BRAF* mutation also reduce benefit from anti-EGFR therapies [6]; therefore, the impact of these mutations on ramucirumab efficacy must be examined as well.

In addition to the possible impact of gene mutations, evidence indicates that the location of the primary CRC has prognostic implications and may be predictive of response to anti-EGFR therapy [7, 8]. This phenomenon may be explained in part by the different embryologic origin of the left and right colon and the resultant anatomical, histological, molecular, and environmental differences that impact tumours arising along its length [7].

Given evidence that additional *RAS/RAF* mutations and tumour sidedness impact EGFR-directed treatment, we undertook retrospective analyses of the association of these parameters and the efficacy of the VEGFR inhibitor, ramucirumab, using data from the RAISE phase III clinical trial.

Methods

Study design

The design of the RAISE phase III trial (ClinicalTrials.gov, NCT01183780) has been reported [1]. In brief, eligible patients had pathologically confirmed mCRC that had progressed during first-line treatment with bevacizumab, oxaliplatin, and a fluoropyrimidine or within 6 months of the last dose of first-line therapy. Patients were randomised (1 : 1) to ramucirumab or placebo, with stratification by geography (North America versus Europe versus all other regions), *KRAS* exon 2 status (wild-type versus mutant), and time to first-line disease progression (≥6 versus <6 months). Ramucirumab (8 mg/kg) or placebo was administered on day 1 of each 2-week cycle, followed by FOLFIRI for both treatment arms. Treatment cycles were continued until disease progression, decision by physician or patient, toxicity, or death.

Tumour tissue collection was undertaken for all study participants. In samples reported locally as *KRAS* wild-type, further *RAS* (*KRAS* exon 3 or 4 mutation, *NRAS* exon 2, 3, or 4 mutation) and *BRAF* mutations were assessed centrally by multiplex qPCR using the Modaplex system (Qiagen) for patients who had sufficient tumour remaining after other biomarker testing [3] was carried out. Patients were classified into one of the three following categories: *BRAF* mutant, *KRAS/NRAS* mutant (*RAS* mutant), or wild-type for *KRAS/NRAS/BRAF* (*RAS/BRAF* wild-type).

Pre-treatment levels of plasma VEGF-D were assessed using an exploratory dual-monoclonal sandwich immunoassay and categorised as high/low (115 pg/ml threshold) as previously described [3].

Sidedness data were collected for each patient. Patients were designated as left CRC with primary tumours originating in the splenic flexure, descending and sigmoid colon, or rectum; and as right CRC with tumours originating in transverse or ascending colon and cecum [7].

Statistical analyses

OS and PFS were evaluated by *RAS/RAF* and tumour sidedness sub-groups using the Kaplan–Meier method. The unstratified Cox proportional hazards model was used to estimate HR and 95% CI. The study stratification factors were used as covariates in the *RAS/RAF* sub-group Cox models. For both OS and PFS, treatment-by-sub-group interaction was examined using the likelihood ratio test. *P*-values were not adjusted for multiple comparisons.

Results

Among the 1072 patients randomised to a treatment arm for the RAISE trial [intent-to-treat (ITT) population], *RAS/RAF* mutation status was available for 912 (85%), and primary tumour location was known for 1012 patients (94%). *RAS* mutations were found in 63% of patients (579/912); *BRAF* mutation in 4.5% (41/912, all

Table 1. Summary of patient and disease characteristics in the *RAS/RAF* mutation sub-groups

	***RAS/BRAF* wild-type**		***RAS* mutant**		***BRAF* mutant[a]**	
	Ramucirumab +FOLFIRI (*N* = 149) *n* (%)	**Placebo +FOLFIRI (*N* = 143) *n* (%)**	**Ramucirumab +FOLFIRI (*N* = 285) *n* (%)**	**Placebo +FOLFIRI (*N* = 294) *n* (%)**	**Ramucirumab +FOLFIRI (*N* = 20) *n* (%)**	**Placebo +FOLFIRI (*N* = 21) *n* (%)**
Age group						
≥65 years	58 (39)	63 (44)	128 (45)	112 (38)	6 (30)	10 (48)
≥70 years	27 (18)	33 (23)	65 (23)	70 (24)	4 (20)	6 (29)
Gender						
Male	82 (55)	102 (71)	150 (53)	161 (55)	12 (60)	12 (57)
Female	67 (45)	41 (29)	135 (47)	133 (45)	8 (40)	9 (43)
Geographical region						
Japan/East Asia	33 (22)	32 (22)	54 (19)	45 (15)	2 (10)	1 (5)
Rest of world	116 (78)	111 (78)	231 (81)	249 (85)	18 (90)	20 (95)
Race						
Black	5 (3)	2 (1)	9 (3)	10 (3)	0	1 (5)
Other	35 (23)	37 (26)	57 (20)	48 (16)	4 (20)	2 (10)
White	108 (72)	103 (72)	219 (77)	234 (80)	16 (80)	17 (81)
Missing	1 (1)	1 (1)	0	2 (1)	0	1 (5)
ECOG PS						
0	80 (54)	72 (50)	142 (50)	147 (50)	13 (65)	11 (52)
1	69 (46)	71 (50)	143 (50)	146 (50)	6 (30)	10 (48)
Missing	0	0	0	1 (<1)	1 (5)	0
Time to progression after first-line						
<6 months	40 (27)	37 (26)	64 (22)	66 (22)	7 (35)	11 (52)
≥6 months	109 (73)	106 (74)	221 (78)	228 (78)	13 (65)	10 (48)
Colorectal tumour sidedness						
Left	110 (74)	108 (76)	178 (62)	175 (60)	7 (35)	6 (29)
Right	29 (19)	27 (19)	95 (33)	99 (34)	11 (55)	14 (67)
Missing	10 (7)	8 (6)	12 (4)	20 (7)	2 (10)	1 (5)
Baseline plasma VEGF-D level[b]						
High	79 (53)	83 (58)	143 (50)	133 (45)	13 (65)	14 (67)
Low	43 (29)	44 (31)	97 (34)	100 (34)	5 (25)	3 (14)
Missing	27 (18)	16 (11)	45 (16)	61 (21)	2 (10)	4 (19)
Baseline plasma CEA level						
>10 ng/ml	90 (60)	97 (68)	195 (68)	196 (67)	13 (65)	9 (43)
≤10 ng/ml	44 (30)	38 (27)	76 (27)	80 (27)	7 (35)	11 (52)
≥200 ng/ml	23 (15)	26 (18)	63 (22)	64 (22)	3 (15)	2 (10)
<200 ng/ml	111 (75)	109 (76)	208 (73)	212 (72)	17 (85)	18 (86)
Missing	15 (10)	9 (6)	14 (5)	18 (6)	0	1 (5)

[a]A single patient was found to have mutations in both *RAS* and *BRAF*; this patient was included only in the *BRAF* mutant sub-group for all summaries and analyses and in the counts listed above.

[b]VEGF-D high ≥115 pg/ml; VEGF-D low <115 pg/ml.

CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; FOLFIRI, folinic acid, 5-fluorouracil and irinotecan; PS, performance status; VEGF, vascular endothelial growth factor.

V600E positive); 32% of patients were *RAS/BRAF* wild-type (292/912) (see flowchart of supplementary Figure S1 and Table S1, available at *Annals of Oncology* online for details). Within *RAS/BRAF* wild-type and *RAS* mutant sub-groups (Table 1), baseline characteristics were balanced between treatment arms, although the *RAS/BRAF* wild-type placebo arm had more males (71% versus 55%) and patients with >10 ng/ml CEA (68% versus 60%) than the ramucirumab arm. Within the 41-patient *BRAF* mutant sub-group, treatment arms were relatively balanced. *BRAF* mutations were more prevalent in right-sided tumours.

Among the tumour sidedness sub-groups, left CRC predominated (69%, 699/1012) (supplementary Table S2, available at *Annals of Oncology* online). Within left versus right sub-groups, baseline patient and tumour characteristics were largely balanced between treatment arms. The left sub-group had a lower percentage of females (40% versus 48%) than the right.

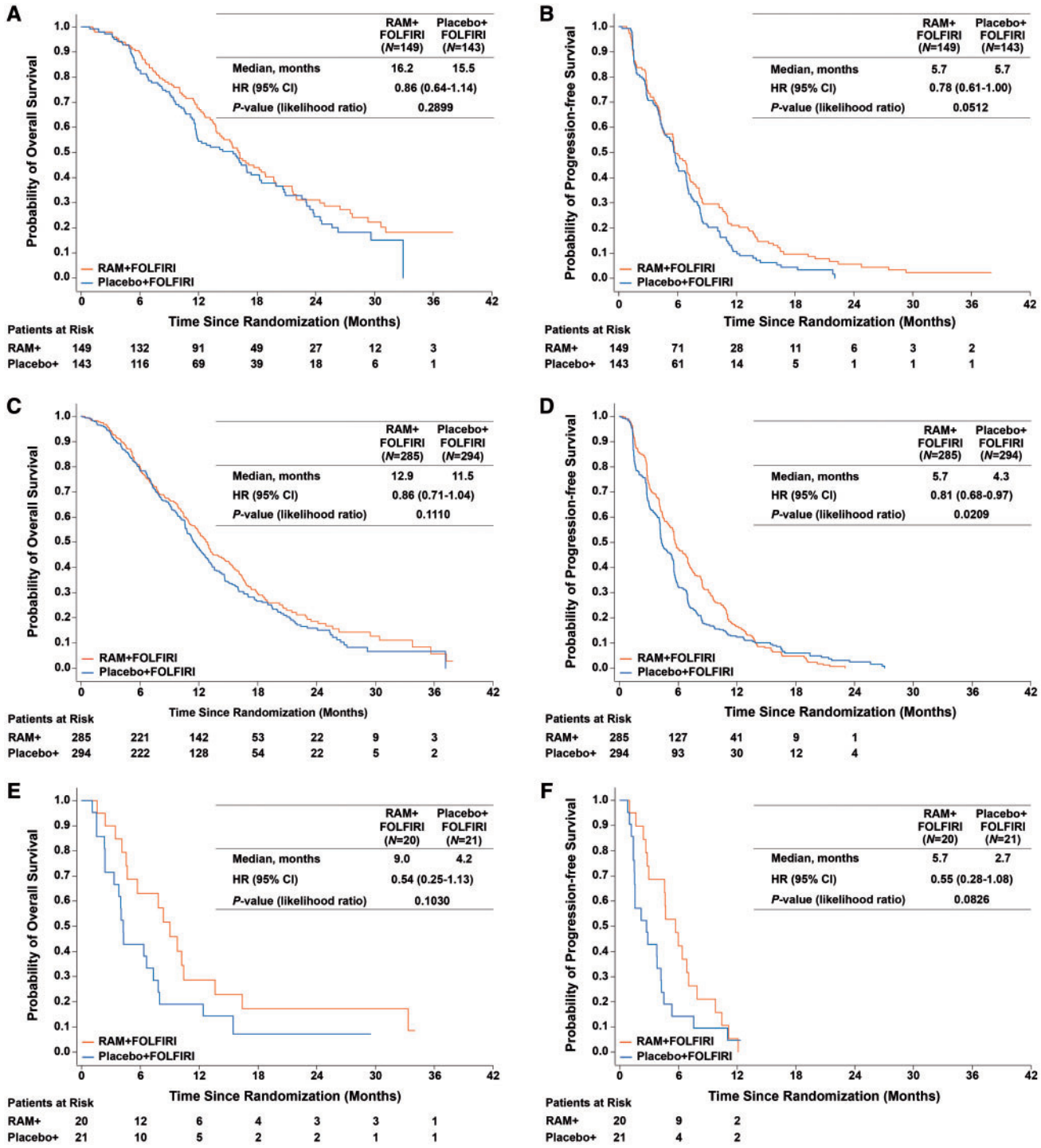

Figure 1. Kaplan–Meier curves of OS and PFS in *RAS/RAF* sub-groups. OS (A, C, E) and PFS (B, D, F) were calculated using Kaplan–Meier plots of RAISE *RAS/BRAF* wild-type (A, B), *RAS* mutant (C, D), and *BRAF* mutant (E, F) populations. HRs and 95% CI were estimated from an unstratified Cox model adjusted for covariates (stratification factors).

A favourable ramucirumab treatment effect was found in the *RAS/BRAF* wild-type sub-group and the *RAS* mutant sub-group. Ramucirumab treatment was associated with prolonged OS (HR < 1) for the *RAS/BRAF* wild-type sub-group (median 16.2 versus 15.5 months; HR = 0.86, 95% CI 0.64–1.14) and the *RAS* mutant sub-group (median 12.9 versus 11.5 months; HR = 0.86, 95% CI 0.71–1.04) (Figure 1A and C; Table 2). A similar trend was observed with PFS for both the *RAS* mutant and *RAS/BRAF*

Table 2. Summary of sub-group analyses of overall survival and progression-free survival by *RAS/RAF* mutation status and tumour sidedness

Sub-group	Treatment arm[a]	*n*	Overall survival			Progression-free survival		
			Median (months)	HR (95% CI) *P*-value[b]	Interaction *P*-value[b]	Median (months)	HR (95% CI) *P*-value[b]	Interaction *P*-value[b]
RAS/BRAF wild-type[c]	Ramucirumab	149	16.2	0.86 (0.64–1.14) *P*=0.2899	0.523	5.7	0.78 (0.61–1.00) *P*=0.0512	0.655
	Placebo	143	15.5			5.7		
RAS mutant[c]	Ramucirumab	285	12.9	0.86 (0.71–1.04) *P*=0.1110		5.7	0.81 (0.68–0.97) *P*=0.0209	
	Placebo	294	11.5			4.3		
BRAF mutant[c]	Ramucirumab	20	9.0	0.54 (0.25–1.13) *P*=0.1030		5.7	0.55 (0.28–1.08) *P*=0.0826	
	Placebo	21	4.2			2.7		
Left-sided CRC	Ramucirumab	353	14.5	0.81 (0.68–0.97) *P*=0.0188	0.276	6.0	0.78 (0.66–0.91) *P*=0.0014	0.578
	Placebo	346	12.0			4.4		
Right-sided CRC	Ramucirumab	154	12.7	0.97 (0.75–1.26) *P*=0.8242		5.6	0.86 (0.67–1.08) *P*=0.1955	
	Placebo	159	11.6			4.5		

[a]Both ramucirumab and placebo were given in combination with FOLFIRI.
[b]Likelihood ratio.
[c]*RAS/RAF* analyses adjusted for stratification factors as covariates.
CI, confidence interval; CRC, colorectal carcinoma; FOLFIRI, folinic acid, 5-fluorouracil and irinotecan; HR, hazard ratio.

wild-type sub-group (Figure 1B and D; Table 2). Treatment-by-mutation status interaction tests indicated that the ramucirumab benefit was not statistically different among the three mutation status sub-groups (OS $P = 0.523$, PFS $P = 0.655$).

Analysis of the Kaplan–Meier plots of the *BRAF* mutant sub-group showed that ramucirumab+FOLFIRI treatment appears to substantially benefit patients harbouring *BRAF*-mutated tumours. Ramucirumab-treated patients exhibited a non-statistically significant OS and PFS benefit over placebo (median OS 9.0 versus 4.2 months, HR = 0.54, 95% CI 0.25–1.13; median PFS 5.7 versus 2.7 months, HR = 0.55, 95% CI 0.28–1.08) (Figure 1E and F; Table 2); although this analysis is limited by sample size. The *RAS/RAF* sub-groups showed no substantial difference between arms in post-discontinuation treatment that may have differentially impacted survival (supplementary Table S3, available at *Annals of Oncology* online).

Since high VEGF-D levels from an exploratory assay seem to suggest a greater benefit with ramucirumab, we examined baseline VEGF-D expression in *RAS/RAF* mutation sub-groups and its association with treatment effects. When treated as a continuous variable, there was no evidence suggesting different VEGF-D expression among the *RAS/BRAF* wild-type, *RAS* mutant, and *BRAF* mutant sub-groups ($P = 0.358$), although *BRAF* mutant population had a slightly higher percentage of patients classified as having high VEGF-D (Table 1). Treatment effects in the *RAS/RAF* mutation sub-groups by baseline plasma VEGF-D levels showed that *RAS* mutants with high baseline VEGF-D levels ($n = 276$) benefitted from ramucirumab with statistically significantly higher OS (HR = 0.64, 95% CI 0.49–0.84, $P = 0.0014$) and PFS (HR = 0.54, 95% CI 0.42–0.70, $P < 0.0001$) (supplementary Table S4, available at *Annals of Oncology* online). In contrast, patients with *RAS* mutations with low baseline VEGF-D ($n = 197$) exhibited no ramucirumab benefit but rather OS and PFS favoured the placebo arm. The *RAS/BRAF* wild-type sub-group behaved similarly to the *RAS* mutant sub-group. Patients with high baseline VEGF-D exhibited a significant PFS benefit from ramucirumab (although no OS benefit was observed), and the low VEGF-D sub-group displayed no benefit from ramucirumab (supplementary Table S4, available at *Annals of Oncology* online). The small number of patients in the *BRAF* mutation sub-group precluded conclusions regarding effect of ramucirumab by VEGF-D level. Stem-and-leaf plots were constructed to examine data distribution by baseline VEGF-D level (supplementary Figure S2, available at *Annals of Oncology* online). In patients with *BRAF* mutations, there was no indication of a differential ramucirumab benefit in patients by VEGF-D level.

The treatment effect of ramucirumab+FOLFIRI by tumour sidedness was also evaluated. Ramucirumab-treated patients with left-sided tumours exhibited improved OS (HR = 0.81, 95% CI 0.68–0.97), with median OS increasing 2.5 months for ramucirumab over placebo (14.5 versus 12.0 months) (Figure 2A; Table 2). Patients with right CRC tumours also exhibited a directional ramucirumab survival benefit on aggregate, but of smaller magnitude, with a 1.1-month increase in median OS (12.7 versus 11.6 months, HR = 0.97, 95% CI 0.75–1.26) (Figure 2C; Table 2). The interaction *P*-value was not statistically significant (0.276), indicating that sidedness is not predictive of the efficacy of adding ramucirumab to FOLFIRI in these analyses. A similar trend was observed with PFS (Figure 2B and D); the interaction *P*-value was again not significant (0.578).

There was no association between VEGF-D levels and sidedness (supplementary Table S5, available at *Annals of Oncology* online); the ramucirumab benefit in patients with high VEGF-D levels was seen in both right- and left-sided tumours (supplementary Table S6, available at *Annals of Oncology* online). There was no substantial difference among the sidedness sub-groups in post-discontinuation treatment that likely would have impacted

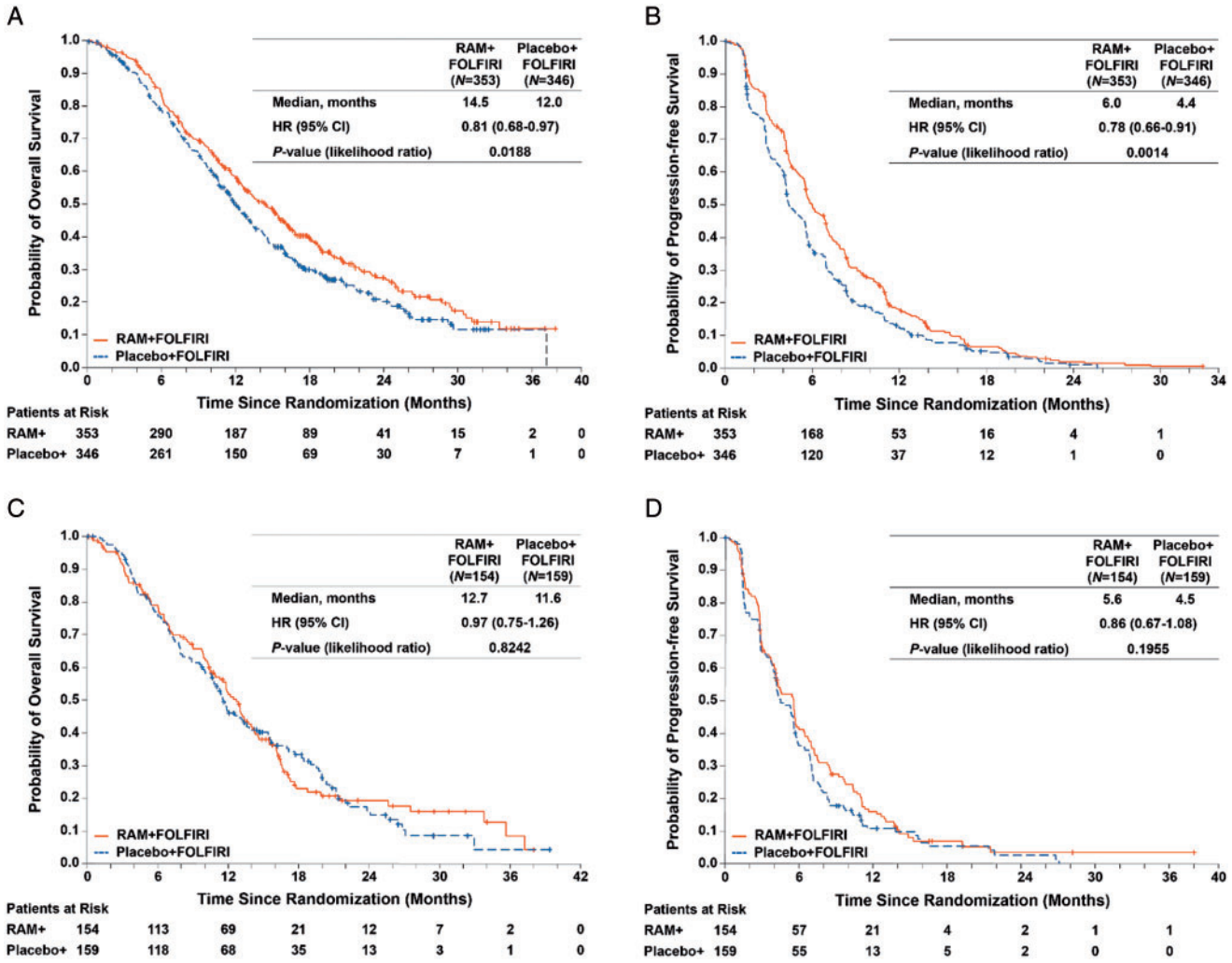

Figure 2. Kaplan–Meier curves of OS and PFS in left and right CRC sub-groups. OS (A, C) and PFS (B, D) were determined using Kaplan–Meier plots of RAISE ITT patients with left (A, B) and right (C, D) CRC. HRs and 95% CI were estimated from an unstratified Cox model with treatment group as the only covariate. Tick marks represent censored events.

survival results (supplementary Table S7, available at *Annals of Oncology* online).

Discussion

Analyses of mCRC trials have revealed that the *RAS/RAF* gene mutation profile and tumour sidedness are both determinants of patient prognosis and have bearing on anti-EGFR treatment efficacy in first-line trials [9, 10]. Published data on the impact of tumour sidedness and *RAS/RAF* mutations on the efficacy of antiangiogenic therapy is limited, especially in the second-line setting. Our exploratory retrospective analyses of the RAISE phase III trial data examined whether *RAS/RAF* mutation status and tumour sidedness influenced the antiangiogenic treatment efficacy of ramucirumab in patients with mCRC that progressed during or after a first-line treatment with bevacizumab, oxaliplatin, and a fluoropyrimidine. While these exploratory analyses are limited because they are retrospective and may be underpowered, they are useful indicators of areas to investigate more completely.

Analysis of patients with *RAS* mutations in the RAISE trial showed these mutations were associated with a worse prognosis than the *RAS/BRAF* wild-type. Other studies have made a similar observation [10]. Consistent with the prior RAISE analysis, this analysis showed ramucirumab added to FOLFIRI improved patient outcomes over placebo regardless of *RAS* mutation status. The ramucirumab benefit to patients with *KRAS/NRAS* mutation could not be ascribed to an imbalance between treatment arms in baseline characteristics, including any imbalance in VEGF-D and CEA baseline plasma levels. However, it was noteworthy that both *RAS* mutant patients and *RAS/BRAF* wild-type patients with high baseline VEGF-D levels displayed a more robust response to ramucirumab treatment than those with low VEGF-D levels, suggesting the predictive value of VEGF-D is independent of the *RAS* mutation status.

In agreement with other studies [10], the RAISE data showed that the *BRAF* mutation was present in a low percentage of patients with CRC (4.5%) and occurred more frequently in right-sided tumours. Patients with the *BRAF* mutation had worse survival than patients who were *RAS/BRAF* wild-type, irrespective of

treatment received, confirming *BRAF* as a negative prognostic factor in the second-line setting. Patients with the *BRAF* mutation appeared to benefit from ramucirumab over placebo (OS HR = 0.54, 95% CI 0.25–1.13; PFS HR = 0.55, 95% CI 0.28–1.08), with median OS and PFS more than double the placebo medians. This result could not be explained by an imbalance between treatment arms in patients with low baseline CEA levels or high baseline VEGF-D levels (Table 1), two variables associated with better ramucirumab efficacy. However, the sample size was too small to make any firm determination about whether there is a real difference in effect in the *BRAF*-mutant patients versus the *RAS/BRAF* wild-type or *RAS* mutant populations. Currently, there is no strong biological rationale for a greater ramucirumab benefit in patients with *BRAF*-mutated mCRC.

The ramucirumab benefit in *BRAF* mutant tumours may differ from that of the anti-EGFR monoclonal antibodies, cetuximab and panitumumab, which appear to have minimal benefit in first-line trials, and a suggestion of harm in one second-line trial (PICCOLO) [10, 11]. The indication of a potentially increased ramucirumab benefit observed with *BRAF*-mutated cancers in the RAISE trial was of interest given the poor prognosis of *BRAF* mutant CRC. These findings are consistent with the VELOUR trial biomarker analysis [12, 13] that analyzed 482 samples from 1226 randomised patients (39% of the patients) in a similar setting: patients with second-line mCRC that progressed after oxaliplatin-based chemotherapy. The trial randomised aflibercept, a fusion protein that binds circulating VEGF-A, VEGF-B, and PlGF, versus placebo, both in combination with FOLFIRI chemotherapy. The *BRAF*-mutated population ($n = 36$, 7.5%) had a numerically stronger benefit with the aflibercept treatment (OS HR = 0.42, 95% CI 0.16–1.09) compared with the aflibercept treatment effect observed in the *RAS* wild-type, *RAS* mutant, and ITT population.

Analysis of primary tumour sidedness distribution in the RAISE trial showed 69% of patients had left-sided tumours and 31% had right-sided. This left-right ratio is comparable to what has been observed in other studies [9, 14]. The left tumour sub-group had a lower percentage of females and mutant *RAS* tumours than the right tumour sub-group, consistent with previously published data [7, 15].

Examination of the survival benefit associated with tumour location revealed patients with left-sided CRC tumours exhibited a significant OS benefit from ramucirumab (2.5 months, HR = 0.81, $P = 0.0188$). The improvement in median OS for patients with right-sided CRC tumours receiving ramucirumab was lesser (1.1 months) and not statistically significant (HR = 0.97, $P = 0.8242$) in this smaller patient sub-group. The PFS results followed the same trend. While the non-significant interaction test for both end points (OS $P = 0.276$; PFS $P = 0.578$) suggests a lack of evidence for different ramucirumab efficacy according to primary tumour site of origin, confirmation of this result would require an appropriately powered, prospectively planned study.

Response to ramucirumab by both patients with left- and right-sided CRC tumours is similar to reported results with bevacizumab in first-line studies [16, 17] and in the maintenance AIO 0207 study [18]. The AIO 0207 study compared fluoropyrimidine plus bevacizumab, bevacizumab alone, and no treatment following 24 weeks of standard induction chemotherapy. Tumour sidedness acted as a strong prognostic factor, but the antiangiogenic benefit was seen on both sides, with a numerically superior antiangiogenic benefit in patients with left-sided tumours. The second-line mCRC VELOUR study also found that addition of an antiangiogenic was efficacious for left- and right-sided tumours [13].

The efficacy of EGFR inhibitors appears to be limited by tumour sidedness. Studies have identified that left CRC tumours seem to be responsive to anti-EGFR therapy (cetuximab, panitumumab), but right-sided tumours are not [14, 19, 20]. Therefore, treatment guidelines currently recommend using these agents only in tumours originating from the left side of the colon [21, 22].

In conclusion, exploratory retrospective analyses of RAISE trial data have shown ramucirumab treatment is effective in a second-line setting, regardless of *RAS/RAF* mutation status and tumour sidedness. While the EGFR inhibitor treatments appear more circumscribed in their effective usage, ramucirumab is effective for patients with mutant *RAS* or *BRAF* tumours and patients who are *RAS/BRAF* wild-type. Of interest, evidence was found that patients with *BRAF* mutant tumours have a potentially increased benefit with ramucirumab, but the relationship was not significant in this small sub-population and requires further validation.

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