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ORIGINAL ARTICLE

Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer: results from two randomized first-line panitumumab studies

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Background: Previous studies have reported the prognostic impact of primary tumor sidedness in metastatic colorectal cancer (mCRC) and its influence on cetuximab efficacy. The present retrospective analysis of two panitumumab trials investigated a possible association between tumor sidedness and treatment efficacy in first-line mCRC patients with *RAS* wild-type (WT) primary tumors.

Materials and methods: Data from two randomized first-line panitumumab trials were analyzed for treatment outcomes by primary tumor sidedness for *RAS* WT patients. PRIME (phase 3; NCT00364013) compared panitumumab plus FOLFOX versus FOLFOX alone; PEAK (phase 2; NCT00819780) compared panitumumab plus FOLFOX versus bevacizumab plus FOLFOX. Primary tumors located in the cecum to transverse colon were coded as right-sided, while tumors located from the splenic flexure to rectum were considered left-sided.

Results: Tumor sidedness ascertainment (*RAS* WT population) was 83% ($n = 559/675$); 78% of patients ($n = 435$) had left-sided and 22% ($n = 124$) had right-sided tumors. Patients with right-sided tumors did worse for all efficacy parameters compared with patients with left-sided disease in the *RAS* WT population and also in the *RAS/BRAF* WT subgroup. In patients with left-sided tumors, panitumumab provided better outcomes than the comparator treatment, including on median overall survival (PRIME: 30.3 versus 23.6 months, adjusted hazard ratio = 0.73, $P = 0.0112$; PEAK: 43.4 versus 32.0 months, adjusted hazard ratio = 0.77, $P = 0.3125$).

Conclusion: The results of these retrospective analyses confirm that in *RAS* WT patients, right-sided primary tumors are associated with worse prognosis than left-sided tumors, regardless of first-line treatment received. *RAS* WT patients with left-sided tumors derive greater benefit from panitumumab-containing treatment than chemotherapy alone or combined with bevacizumab, including an overall survival advantage (treatment difference: PRIME 6.7 months; PEAK 11.4 months). No final conclusions regarding optimal treatment could be drawn for *RAS* WT patients with right-sided mCRC due to the relatively low number of paxtients. Further research in this field is warranted.

Trial registration (Clinicaltrials.gov): PRIME (NCT00364013), PEAK (NCT00819780).

Key words: panitumumab, tumor sidedness, *RAS* wild-type, metastatic colorectal cancer, first-line

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide with over 1.3 million new diagnoses and 694 000 deaths in 2012 [1]. During the last decade, with improvements in treatment strategies such as the implementation of chemotherapy and new biological agents [2], median survival has increased from 12 to up to 30 months for some patients with metastatic CRC (mCRC) [3, 4].

Recently, *RAS* mutations (*KRAS* and *NRAS* exons 2/3/4) have been shown to be associated with lack of response to anti-epidermal growth factor receptor (EGFR) therapy [5]. Therefore, guidelines now recommend that *RAS* wild-type (WT) tumor status should be confirmed before starting this treatment [6]. However, additional biomarkers are still needed as not all *RAS* WT patients respond to anti-EGFR therapy. HER2 amplification has been reported as a mechanism of resistance to anti-EGFR treatment and therapeutic approaches for patients with HER2-positive mCRC tumors are in development [7]. *BRAF* V600E mutations, harbored by ∼10% of tumors, confer poor prognosis in mCRC [8]. However, results from two recent meta-analyses [9, 10] have generated opposing conclusions suggesting that data are currently insufficient to definitively exclude efficacy of panitumumab or cetuximab in patients with *RAS* WT/*BRAF* V600E-mutated tumors and that more research is needed.

Right-sided colon tumors have a lower incidence, are more prevalent in females, more frequently carry *BRAF* mutations, have a higher tumor/nodes/metastases stage at presentation, and are associated with worse prognosis than left-sided colorectal tumors [11–13]. A possible explanation for these differences is the different embryological origin of the proximal and distal parts of the colon and colorectum. Both parts are joined together at the proximal two-thirds and distal one-third of the transverse colon and have different blood supplies, innervations and lymphatic drainages [11]. Moreover, tumor sidedness correlates with different biological and molecular characteristics [11, 14].

There have been communications reporting the efficacy of biological agents in mCRC according to primary tumor sidedness [14–17]. Notably retrospective analyses of two first-line studies comparing chemotherapy plus cetuximab against chemotherapy plus bevacizumab reported better results for cetuximab in patients with left-sided tumors [15–17]. In contrast, patients with right-sided tumors generally appeared to benefit more from chemotherapy plus bevacizumab. No publications to date have investigated the effect of tumor sidedness on panitumumab efficacy. The aim of these retrospective analyses was to investigate the possible association between tumor sidedness and panitumumab efficacy in patients with *RAS* WT mCRC undergoing first-line treatment in two randomized clinical trials.

Materials and methods

Study design and data sources

These retrospective analyses included data from two published randomized controlled first-line mCRC trials. PRIME (NCT00364013) was a phase 3 study assessing the efficacy of panitumumab plus FOLFOX compared with FOLFOX alone [5, 18]. PEAK (NCT00819780) was a randomized phase 2 study of panitumumab plus FOLFOX or bevacizumab plus FOLFOX [19, 20].

Assessment of tumor sidedness

Information on tumor sidedness was obtained from the free-text surgery descriptions included in the case report forms and from the original pathology reports. Primary tumors located in the cecum to transverse colon were coded as right-sided. Tumors located from the splenic flexure to rectum were categorized as left-sided. The assessors of tumor sidedness were blinded to *RAS* and *BRAF* mutation status, treatment allocation and clinical outcomes.

Study population

The primary analysis was carried out on the *RAS* WT (*KRAS*/*NRAS* exon 2/3/4 WT) population in order to study the effect of tumor sidedness on clinical outcomes in panitumumab-treated mCRC patients. The prognostic impact of tumor side was also assessed after excluding all *BRAF* V600E mutant (MT) patients from the *RAS* WT cohort (i.e. in the *RAS*/*BRAF* WT population).

Statistical analyses

As these were retrospective analyses, no formal hypothesis testing was planned. The efficacy endpoints evaluated were response rate (RR), duration of response (DoR), progression-free survival (PFS) and overall survival (OS).

DoR was calculated from first confirmed response to first occurrence of progressive disease (PD) per modified Response Evaluation Criteria In Solid Tumors (RECIST). PFS was calculated from randomization to PD per modified RECIST or death (whichever occurred first). Patients not meeting these criteria at the analysis data cut-off had their DoR or PFS censored at the last evaluable disease assessment. OS was calculated from randomization to death. Patients who had not died by the analysis data cut-off had their time of death censored at the last contact date on which they were known to be alive.

All data were summarized descriptively. The treatment hazard ratio (HR) for panitumumab relative to FOLFOX alone or to bevacizumab in combination with FOLFOX and the associated 95% confidence intervals (CI) were estimated from a stratified Cox proportional hazard model (Wald tests to generate *P*-values). For the *RAS* WT analysis set, the Cox model was adjusted for *BRAF* status, previous adjuvant therapy and baseline Eastern Cooperative Oncology Group (ECOG) score. HRs below one favor the panitumumab arm. Kaplan–Meier curves were generated for all time-to-event end points.

Results

Patient population

Overall, the sidedness of the primary tumor could be determined unequivocally in 83% (559/675) of patients from the *RAS* WT populations of PRIME and PEAK. Most of these patients had left-sided primary tumors (79% and 75%).

In the overall *RAS* WT population ($n = 559$), *BRAF* V600E mutations were present in 5% and 2% of left-sided mCRC patients in PRIME and PEAK, while 33% and 28% of patients with right-sided mCRC were *BRAF* MT, respectively (Table 1). In PEAK, there was an imbalance by treatment arm in patients with right-sided disease with 7% ($n = 1$) versus 41% ($n = 9$) of those in the bevacizumab versus panitumumab arm, respectively

Table 1. Baseline demographics and disease characteristics of the *RAS* WT population

Baseline characteristic		PRIME				PEAK			
		Pmab arm		Comparator arm		Pmab arm		Comparator arm	
		Left	Right	Left	Right	Left	Right	Left	Right
	Patient number	169	39	159	49	53	22	54	14
Baseline ECOG, *n* (%)	Missing	–	–	1 (0.6)	–	–	–	–	–
	0	106 (62.7)	22 (56.4)	88 (55.3)	27 (55.1)	37 (69.8)	10 (45.5)	35 (64.8)	9 (64.3)
	1	56 (33.1)	15 (38.5)	61 (38.4)	19 (38.8)	16 (30.2)	12 (54.5)	19 (35.2)	5 (35.7)
	2	7 (4.1)	2 (5.1)	9 (5.7)	3 (6.1)	–	–	–	–
Prior adjuvant chemotherapy, *n* (%)	No	140 (82.8)	29 (74.4)	133 (83.6)	39 (79.6)	45 (84.9)	18 (81.8)	41 (75.9)	10 (71.4)
	Yes	29 (17.2)	10 (25.6)	26 (16.4)	10 (20.4)	8 (15.1)	4 (18.2)	13 (24.1)	4 (28.6)
Sex, *n* (%)	Female	49 (29.0)	18 (46.2)	56 (35.2)	24 (49.0)	19 (35.8)	7 (31.8)	16 (29.6)	4 (28.6)
	Male	120 (71.0)	21 (53.8)	103 (64.8)	25 (51.0)	34 (64.2)	15 (68.2)	38 (70.4)	10 (71.4)
BRAF status, *n* (%)	Test failure	6 (3.6)	0 (0.0)	3 (1.9)	1 (2.0)	–	–	–	–
	Mutant	7 (4.1)	13 (33.3)	8 (5.0)	16 (32.7)	1 (1.9)	9 (40.9)	1 (1.9)	1 (7.1)
	Wild-type	156 (92.3)	26 (66.7)	148 (93.1)	32 (65.3)	52 (98.1)	13 (59.1)	53 (98.1)	13 (92.9)
Sites of metastasis, *n* (%)	Liver+other	119 (70.4)	21 (53.8)	108 (67.9)	35 (71.4)	21 (39.6)	13 (59.1)	21 (38.9)	9 (64.3)
	Liver only	33 (19.5)	6 (15.4)	31 (19.5)	5 (10.2)	18 (34.0)	4 (18.2)	15 (27.8)	4 (28.6)
	Other only	17 (10.1)	12 (30.8)	20 (12.6)	9 (18.4)	14 (26.4)	5 (22.7)	18 (33.3)	1 (7.1)
Age, years (range)	Median	61 (27, 81)	62 (42, 80)	62 (27, 82)	61 (24, 78)	60 (23, 77)	64 (43, 82)	60 (39, 82)	66 (50, 78)

ECOG, Eastern Cooperative Oncology Group; *n*, number; Pmab, panitumumab.

having *BRAF* MT mCRC. Median age was similar between patients with left- and right-sided mCRC.

Prognostic effect of primary tumor sidedness

RAS WT patients with left-sided tumors had better OS, PFS, RR and DoR outcomes compared with those with right-sided tumors, irrespective of treatment received (Table 2; Figure 1). The OS HRs consistently demonstrated worse prognosis for patients with right-sided tumors (supplementary Table S1, available at *Annals of Oncology* online).

After excluding *BRAF* MT patients from the *RAS* WT cohort, prognosis remained poor in patients with *RAS*/*BRAF* WT right-sided mCRC compared with those with left-sided mCRC for each treatment arm (Table 3).

Predictive effect on OS and PFS of primary tumor sidedness in *RAS* WT patients

The effect of primary tumor sidedness on OS and PFS outcomes in *RAS* WT patients is shown in Table 2 and Figure 1. In PRIME, *RAS* WT patients with left-sided tumors benefited from the addition of panitumumab to FOLFOX, as indicated by longer median OS (30.3 versus 23.6 months, adjusted HR = 0.73, $P = 0.0112$) and PFS (12.9 versus 9.2 months, adjusted HR = 0.72, $P = 0.0048$), compared with patients treated with FOLFOX alone. No significant differences in median OS or PFS were observed in patients with right-sided mCRC (OS: 11.1 versus 15.4 months, adjusted HR = 0.87, $P = 0.5398$; PFS: 7.5 versus 7.0 months, adjusted HR = 0.80, $P = 0.3286$).

In PEAK, *RAS* WT patients with left-sided primary tumors had numerically better median OS (43.4 versus 32.0 months, adjusted HR = 0.77, $P = 0.3125$) and PFS (14.6 versus 11.5 months, adjusted HR = 0.68, $P = 0.0732$) in the panitumumab versus bevacizumab arm. In patients with right-sided tumors, the adjusted HR for OS favored panitumumab while the PFS HR favored bevacizumab (OS: 17.5 versus 21.0 months, HR = 0.67, $P = 0.3239$; PFS: 8.7 versus 12.6 months, HR = 1.04, $P = 0.9085$). Despite the adjusted HR, the right-sided comparison should be evaluated with caution, as it was based on very few patients.

Effect of primary tumor sidedness on RR and DoR in the *RAS* WT population

In the PRIME trial, the RR was higher in the panitumumab arm versus FOLFOX alone in patients with both left-sided (68% versus 53%) and right-sided (42% versus 35%) tumors. DoR was also longer in the panitumumab arm than in the control arm on both sides (Table 2).

In the PEAK trial, a higher RR was also seen for panitumumab versus bevacizumab in patients with both left-sided (64% versus 57%) and right-sided (64% versus 50%) tumors. Longer median DoR was seen for panitumumab plus FOLFOX versus bevacizumab plus FOLFOX in patients with left-sided tumors (16.1 versus 9.5 months), while no difference was seen in patients with right-sided disease (8.7 versus 9.2 months).

Predictive effect on OS and PFS of primary tumor sidedness in *RAS*/*BRAF* WT patients

In PRIME, *RAS*/*BRAF* WT patients with left-sided tumors benefited from the addition of panitumumab to FOLFOX, as indicated by longer median OS (32.5 versus 23.6 months, adjusted HR = 0.68, $P = 0.0027$) and PFS (12.9 versus 9.3 months,

Table 2. Efficacy outcomes in the *RAS* WT population

Study	Treatment	*n* patients		OS (m)		PFS (m)		RR (%)		DoR (m)	
		Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
PRIME	Pmab+ FOLFOX	169/168[a]	39/ 38[a]	30.3 (25.8, 36.1)	11.1 (8.1, 25.2)	12.9 (10.0, 14.6)	7.5 (5.5, 10.4)	67.9	42.1	11.8 (9.6, 14.8)	9.7 (3.9, 13.3)
	FOLFOX	159/156[a]	49/46[a]	23.6 (18.2, 26.9)	15.4 (9.1, 21.7)	9.2 (7.6, 10.7)	7.0 (5.4, 8.0)	52.6	34.8	9.3 (7.7, 11.0)	7.6 (4.2, 9.4)
	Adjusted HR[b]			0.73 (0.57, 0.93)	0.87 (0.55, 1.37)	0.72 (0.57, 0.90)	0.80 (0.51, 1.26)	1.91[c] (1.18, 3.07)	1.36[c] (0.51, 3.62)		
	P-value			0.0112	0.5398	0.0048	0.3286	–	–		
PEAK	Pmab+ FOLFOX	53/ 53[a]	22/ 22[a]	43.4 (31.6, 63.0)	17.5 (9.1, 30.7)	14.6 (11.6, 17.7)	8.7 (5.7, 10.9)	64.2	63.6	16.1 (11.1, 20.9)	8.7 (3.7, 14.2)
	Bmab+ FOLFOX	54/ 54[a]	14/ 14[a]	32.0 (26.0, 47.4)	21.0 (6.0, 29.0)	11.5 (9.3, 13.0)	12.6 (1.8, 16.6)	57.4	50.0	9.5 (7.9, 13.8)	9.2 (5.9, 16.6)
	Adjusted HR[b]			0.77 (0.46, 1.28)	0.67 (0.30, 1.50)	0.68 (0.45, 1.04)	1.04 (0.50, 2.18)	1.33[c] (0.57, 3.11)	1.75[c] (0.36, 8.39)		
	P-value			0.3125	0.3239	0.0732	0.9085	–	–		

[a]Number of patients assessable for response.
[b]Adjusted treatment HR calculated from model with factors for *BRAF* status, prior adjuvant therapy and baseline ECOG. HR below 1 favors pmab arm (PRIME, PEAK).
[c]Odds ratio for treatment difference in RR presented. An odds ratio >1 favors the pmab arm (PRIME, PEAK).
Bmab, bevacizumab; DoR (m), duration of response in months; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; *n*, number; OS (m), overall survival in months; PFS (m), progression-free survival in months; Pmab, panitumumab; RR, response rate.

Table 3. Efficacy outcomes in the *RAS/BRAF* WT population

Study	Treatment	*n* Patients		OS (m)		PFS (m)	
		Left	Right	Left	Right	Left	Right
PRIME	Pmab+FOLFOX	156	26	32.5 (27.5, 37.6)	22.5 (8.1, 30.8)	12.9 (10.0, 14.9)	8.9 (5.5, 11.3)
	FOLFOX	148	32	23.6 (18.2, 27.7)	21.5 (10.8, 26.0)	9.3 (7.7, 10.8)	7.3 (4.2, 11.1)
	Adjusted HR[a]			0.68 (0.52, 0.87)	0.97 (0.55, 1.74)	0.69 (0.54, 0.88)	0.75 (0.42, 1.33)
	P-value			0.0027	0.9295	0.0028	0.3260
PEAK	Pmab+FOLFOX	52	13	43.4 (34.2, 63.0)	22.5 (8.4, 36.9)	14.6 (11.6, 18.1)	10.3 (6.1, 11.6)
	Bmab+FOLFOX	53	13	32.0 (26.9, 48.5)	23.3 (6.0, 29.0)	11.5 (9.3, 13.0)	12.6 (1.8, 18.4)
	Adjusted HR[b]			0.76 (0.45, 1.27)	0.64 (0.26, 1.58)	0.65 (0.43, 1.00)	0.90 (0.39, 2.07)
	P-value			0.2945	0.3326	0.0514	0.8092

[a]Adjusted treatment HR calculated from model with factors for region and baseline ECOG. HR below 1 favors the pmab arm (PRIME).
[b]Adjusted treatment HR calculated from model with factors for prior adjuvant oxaliplatin therapy. HR below 1 favors the pmab arm (PEAK).
Bmab, bevacizumab; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; *n*, number; OS (m), overall survival in months; PFS (m), progression-free survival in months; Pmab, panitumumab.

adjusted HR = 0.69, $P = 0.0028$), compared with FOLFOX alone (Table 3). No significant differences in median OS (22.5 versus 21.5 months, adjusted HR = 0.97, $P = 0.9295$) or PFS (8.9 versus 7.3 months, adjusted HR = 0.75, $P = 0.3260$) were observed in patients with right-sided mCRC.

In PEAK, *RAS/BRAF* WT patients with left-sided tumors had numerically better median OS (43.4 versus 32.0 months, adjusted HR = 0.76, $P = 0.2945$) and PFS (14.6 versus 11.5 months, adjusted HR = 0.65, $P = 0.0514$) in the panitumumab versus bevacizumab arm. In patients with right-sided tumors, median OS was 22.5 versus 23.3 months (adjusted HR = 0.64, $P = 0.3326$) and PFS was 10.3 versus 12.6 months (adjusted HR = 0.90, $P = 0.8092$) in the panitumumab versus bevacizumab arm, respectively.

Discussion

This is the first publication reporting the effect of primary tumor sidedness on clinical outcomes during panitumumab treatment. Data from two randomized first-line panitumumab mCRC trials were retrospectively analyzed according to tumor sidedness.

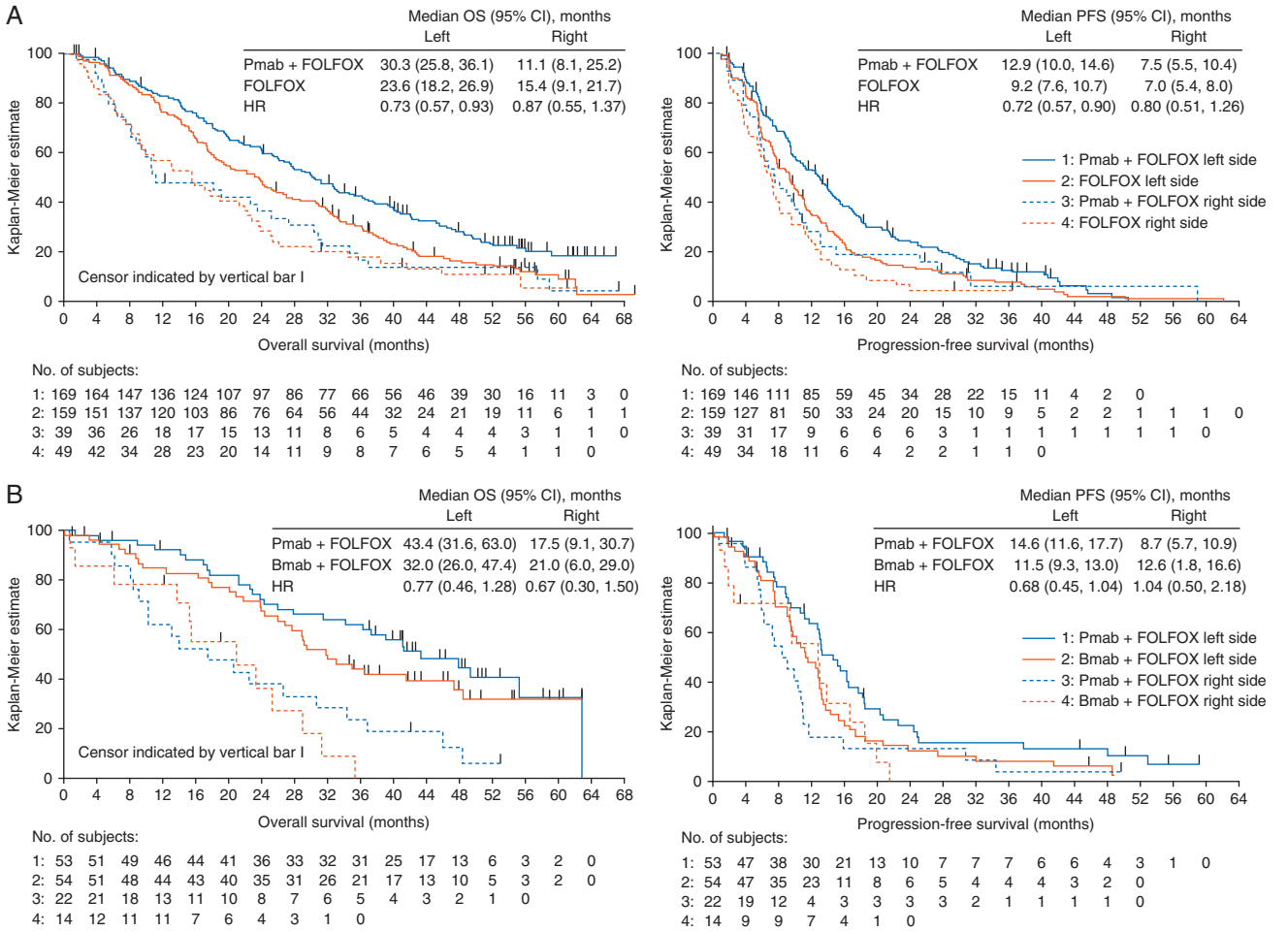

Figure 1. Overall survival and progression-free survival in the *RAS* WT populations for (A) PRIME and (B) PEAK. Bmab, bevacizumab; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; Pmab, panitumumab.

These analyses confirmed the prognostic effect of tumor sidedness in patients with *RAS* WT and *RAS/BRAF* WT mCRC, in line with data previously reported in the literature [12, 15, 17, 21, 22]. Regardless of first-line treatment received, *RAS* WT patients with right-sided tumors had worse prognosis than those with left-sided tumors. In a second analysis, we excluded all *BRAF* V600E MT patients to evaluate whether the prognostic effect still stood in a first-line *RAS*/*BRAF* WT population. This is important as *BRAF* mutations negatively impact survival and are more frequently present in right- than left-sided tumors [14, 23, 24]. In our population <5% of patients with left-sided mCRC had *BRAF* mutations, while these mutations were present in 28%–33% of right-sided mCRC patients. Considering the high proportion of *BRAF* mutations in patients with right-sided tumors, median OS is clearly better once patients with these mutations are removed from the analysis, supporting the prognostic relevance of *BRAF* in this subgroup of patients with right-sided mCRC. However, in the *RAS*/*BRAF* WT population, right-sided primary tumors were still linked to poorer prognosis compared with left-sided primary tumors, corroborating previously reported work [21, 23].

Regarding the predictive effect of tumor sidedness on efficacy of anti-EGFR therapy, most recent data comes from first-line studies comparing chemotherapy with either bevacizumab or cetuximab. In the re-analysis of CALGB/SWOG 80405 according to tumor sidedness, OS and PFS were prolonged in the cetuximab arm in *RAS* WT patients with left-sided tumors [16, 17]. Conversely, patients with right-sided tumors had better outcomes in the bevacizumab arm; however, no *BRAF* data from CALGB/SWOG 80405 have been presented and, as we have seen in our own results, imbalances in the proportion of patients with this biomarker can impact median OS. At the time of writing, results from the CALGB trial have not yet been fully published. Therefore, caution should be used when reviewing these data as significant open questions remain, such as treatment exposure and use of post-PD therapy in each arm. Considering the other phase 3 trial comparing cetuximab plus chemotherapy with bevacizumab plus chemotherapy in first-line mCRC (FIRE-3), a retrospective analysis showed similar results, both in terms of the prognostic and predictive impact (left-sided tumors had better prognosis compared with right-sided tumors regardless of treatment; cetuximab was better than bevacizumab in left-sided disease, bevacizumab better in right-sided) [15, 25]. Another recent communication revealed that the primary tumor side's association with OS and PFS during cetuximab treatment did not remain significant after multivariate analysis adjusting for an extensive biomarker panel, suggesting that mutations in *BRAF* and *NRAS*, tumor methylation and (perhaps) gene expression patterns may account for the observed effect [26].

Here we report that patients with left-sided primary tumors benefit from the addition of panitumumab to chemotherapy in

the first-line PRIME and PEAK trials. *RAS* WT patients with left-sided tumors in the panitumumab arm had better OS (6.7 and 11.4 months difference respectively), PFS (3.7 and 3.1 months difference, respectively), RRs (15.3 and 6.8 absolute difference in percentage points) and DoR (2.5 and 6.6 months difference) than the chemotherapy arm, with or without bevacizumab. These findings are in line with results from other recent studies [15, 16].

In *RAS* WT patients with right-sided tumors, numerically higher RRs were observed in patients receiving panitumumab compared with comparator treatments, again, consistent with other communicated findings [15, 16]. For OS and PFS in the *RAS* WT right-sided population, most medians were better in the control arm. In relation to imbalances in baseline characteristics, adjusted OS HRs (calculated from a model including *BRAF* status, prior adjuvant chemotherapy and baseline ECOG) were in favor of the panitumumab arms, although *P*-values were not significant. However, results for patients with right-sided primary tumors have to be taken with caution due to the small sample sizes and small absolute differences between arms.

A limitation of our study is the retrospective exploratory nature of these analyses. Therefore, our population is not controlled for subgroup imbalances. This was partially tackled by adjusting the HR calculations. In addition, we have no data on other biomarkers beyond *RAS* and *BRAF*, such as microsatellite instability or methylation, which might also affect clinical outcomes. A strength of this study was the high tumor sidedness ascertainment, which was blinded to allocated treatment and clinical outcome. In addition, there was a high *RAS*/*BRAF* ascertainment rate and the analyses were carried out on clean data from two published randomized clinical trials, one of which was conducted with registrational intent.

In summary, first-line panitumumab plus chemotherapy provided better OS, PFS and RRs compared with first-line chemotherapy with or without bevacizumab in *RAS* WT patients with left-sided primary tumors in these two studies. These results consolidate evidence from other trials suggesting anti-EGFR therapy plus chemotherapy as being the preferred first-line treatment option for left-sided mCRC. In patients with right-sided disease, the data are inconclusive and based on the present analyses it is not possible to draw definitive conclusions on optimum treatment. Further research on biomarkers is warranted to identify a potential subgroup of patients with right-sided mCRC who might benefit from panitumumab.

It is clear that proximal and distal CRC should be considered as different clinical entities and tumor sidedness should be considered when making treatment decisions. It should also be included as a stratification factor in future randomized clinical trials, including those assessing impact of treatment sequence, which may also influence long-term outcome. Tumor sidedness is a simple variable, which cannot replace molecular characterization of the tumor but may in part stand as a surrogate for complex and still partially understood tumor biology and thus aid clinical decision-making.

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Disclosure

NB, KOdB, and GVC have no conflicts of interest. RK is an employee of Amgen Ltd. CR has received research funding (institutional) from Novartis and Sanofi, has acted as a consultant for Mylan and Oncompass, and has undertaken speaking engagements for Boehringer Ingelheim, MSD and Novartis. SS is a member of advisory boards for Amgen, Bayer, Celgene, Eli Lilly, Merck, Merrimack, Novartis, Roche and Sanofi. JT has had advisory roles for Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Lilly, MSD, Merck Serono, Novartis, Pfizer, Roche, Sanofi, Symphogen, Taiho and Takeda. JYD has participated in steering committees on behalf of Amgen and Bayer, participated in advisory boards, symposia and acted as a consultant for Amgen, Merck Serono, Roche, Sirtex and Takeda, participated in advisory boards for Boehringer Ingelheim and Sanofi and received research funding from Merck Serono. TA acted as a consultant for Amgen, Bristol-Myers Squibb and Roche, and has had advisory roles for Bayer, Boehringer Ingelheim, Celgene, Eli Lilly, Novartis, Roche, Sanofi Aventis and Xbiotech. MP has received research funding and acted in consultancy/advisory roles for Amgen, received research funding from Roche and Sirtex, and received research funding and participated in symposia for Merck Serono and Servier.

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