Effect of Primary Tumor Location on Second- or Later-line Treatment Outcomes in Patients With RAS Wild-type Metastatic Colorectal Cancer and All Treatment Lines in Patients With RAS Mutations in Four Randomized Panitumumab Studies

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Original Study

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Effect of Primary Tumor Location on Second- or Later-line Treatment Outcomes in Patients With *RAS* Wild-type Metastatic Colorectal Cancer and All Treatment Lines in Patients With *RAS* Mutations in Four Randomized Panitumumab Studies

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Abstract

The results from the retrospective analyses of data from 4 phase III randomized panitumumab trials showed a worse prognosis for patients with right- versus left-sided *RAS* wild-type metastatic colorectal cancer (mCRC) receiving second-line or greater therapy. Furthermore, the addition of panitumumab to standard treatment provided benefit to patients with left-sided *RAS* wild-type tumors. Further research is needed to define the optimal treatment of *RAS* mutant and right-sided *RAS* wild-type mCRC.

Background: The primary tumor location has a prognostic impact in metastatic colorectal cancer (mCRC). We report the results from retrospective analyses assessing the effect of tumor location on prognosis and efficacy of second- and later-line panitumumab treatment in patients with *RAS* wild-type (WT) mCRC and on prognosis in all lines of treatment in patients with *RAS* mutant (MT) mCRC. **Patients and Methods:** *RAS* WT data (n = 483) from 2 randomized phase III panitumumab trials (ClinicalTrials.gov identifiers, NCT00339183 and NCT00113763) were analyzed for treatment outcomes stratified by tumor location. The second analysis assessed the effect of tumor location in *RAS* MT patients (n = 1205) from 4 panitumumab studies (ClinicalTrials.gov identifiers, NCT00364013, NCT00819780, NCT00339183, and NCT00113763). Primary tumors located in the cecum to transverse colon were coded as right-sided; those located from the splenic flexure to the rectum were coded as left-sided. **Results:** Of all patients, the tumor location was ascertained for 83% to 88%; 71% to 77% of patients had left-sided tumors. *RAS* WT patients with right-sided tumors did worse for all efficacy parameters compared with those with left-sided tumors. The patients with left-sided tumors had better outcomes with panitumumab than with the comparator treatment. Because of the low patient numbers, no conclusions could be drawn for right-sided mCRC. The prognostic effect of tumor location on survival was unclear for *RAS* MT patients. **Conclusion:** These retrospective analyses have confirmed that *RAS* WT right-sided mCRC is associated with a poor prognosis, regardless of the treatment. *RAS* WT patients with left-sided tumors benefitted from the addition of panitumumab in second or later treatment lines. Further research is warranted to determine the optimum management of right-sided mCRC and *RAS* MT tumors.

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Introduction

The idea that tumor location had a link with disease biology arose in 1990, when Bufill[1] described colorectal cancer (CRC) by the primary tumor location. Right-sided colon tumors more frequently harbor *BRAF* mutations, have a higher tumor/nodes/metastases stage at presentation, and have a worse prognosis compared with left-sided colorectal tumors.[2,3] The fact that the proximal part of the colon is derived from the embryologic midgut, and the distal part and rectum are derived from the embryologic hindgut might help explain the observed differences.

Several retrospective analyses have assessed the clinical effect of epidermal growth factor receptor (EGFR)-targeted agents in patients with metastatic CRC (mCRC) according to the primary tumor location,[4-7] most of which evaluated first-line data from cetuximab trials.[5-7] These analyses reported better results for cetuximab plus chemotherapy versus chemotherapy alone or combined with bevacizumab in patients with left-sided mCRC.[5-7] In contrast, patients with right-sided tumors generally appeared to benefit more from chemotherapy combined with bevacizumab. Few data are available on the effect of the tumor location on the efficacy of later-line treatment or in patients with *RAS* mutant (MT) mCRC. Also, no studies to date have investigated the effect of tumor location on panitumumab efficacy in these settings. The first aim of the present retrospective analyses was to investigate the possible association between primary tumor location and second- or later-line panitumumab efficacy in patients with *RAS* wild-type (WT) mCRC. The second aim was to assess the effect of tumor location in patients with *RAS* MT tumors.

Patients and Methods

Study Design and Data Sources

The first analysis was performed on the *RAS* (*KRAS* and *NRAS* exon 2, 3, and 4) WT populations from 2 randomized phase III mCRC trials. The second-line 20050181 trial (ClinicalTrials.gov identifier, NCT00339183) evaluated the effect of panitumumab plus FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) compared with FOLFIRI alone.[8,9] The later-line 20020408 trial (ClinicalTrials.gov identifier, NCT00113763) evaluated panitumumab plus best supportive care (BSC) versus BSC alone for patients in whom the available treatment options had failed.[10,11] This analysis assessed the effect of tumor location on clinical outcomes in the *RAS* WT and *RAS/BRAF* WT (after exclusion of all *BRAF* V600E MT patients) populations. The second analysis studied differences in the clinical outcomes for *RAS* MT patients with left- and right-sided mCRC from the 2 cited studies and from 2 additional first-line trials: PRIME (ClinicalTrials.gov identifier, NCT00364013), a phase III trial comparing panitumumab plus FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin) versus FOLFOX alone,[12] and PEAK (ClinicalTrials.gov identifier, NCT00819780), a phase II trial comparing panitumumab plus FOLFOX versus bevacizumab plus FOLFOX.[13]

Assessment of Tumor Location

Tumor location information was obtained from the free-text surgery descriptions included in the case report forms and 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 the tumor location were unaware of the *RAS* and *BRAF* mutation status, treatment allocation, and clinical outcomes.

Statistical Analysis

Because these were exploratory, retrospective analyses, no formal hypothesis testing was planned. The efficacy endpoints evaluated were the response rate (RR), duration of response (DoR), progression-free survival (PFS), and overall survival (OS). These endpoints were calculated as previously reported.[14]

Data were summarized descriptively. The treatment hazard ratio (HR) for the panitumumab arm relative to the comparator arms and the associated 95% confidence intervals were estimated from a stratified Cox proportional hazard model. Wald tests were used to generate *P* values. For the *RAS* WT analysis, the Cox model was adjusted for *BRAF* status, previous adjuvant therapy, and baseline Eastern Cooperative Oncology Group (ECOG) score (study 20050181) or for *BRAF* status and baseline ECOG (study 20020408). For the *RAS* MT analysis, the Cox model was adjusted for the stratification variables as described in the respective study protocols, including region and baseline ECOG (PRIME and study 20020408), previous adjuvant oxaliplatin therapy (PEAK), and region, baseline ECOG, and previous oxaliplatin exposure (study 20050181). No adjustments for *BRAF* status were made in this population because *RAS* and *BRAF* mutations are generally mutually exclusive. Kaplan-Meier curves were generated for all time-to-event endpoints.

Results

Patient Population

The primary tumor location could be determined unequivocally in > 80% of patients in each study (PRIME, 874 of 1049 [83%]; PEAK, 197 of 228 [86%]; 20050181, 887 of 1011 [88%]; 20020408, 290 of 349 [83%]). Approximately three quarters of the patients with the side ascertainable had left-sided mCRC (Supplemental Table 1; available in the online version). In general, the left/right distribution seen in the *RAS* WT and *RAS* MT populations was similar to that in the overall study population. However, in the *RAS* MT population of PEAK, 39% of patients had right-sided mCRC. This *RAS* MT subgroup was markedly smaller in this study because enrollment in PEAK was restricted to *KRAS* exon 2 WT patients.

In the *RAS* WT populations of studies 20050181 (n = 368) and 20020408 (n = 115), *BRAF* V600E mutations were present in 4% and 6% of patients with left-sided mCRC compared with 31% and 20% of right-sided mCRC patients. No difference was found in age between the left- and right-sided mCRC patients in either the *RAS* WT (Table 1) or *RAS* MT (Table 2) populations.

Prognostic Effect of Primary Tumor Location

RAS WT. In the 20050181 and 20020408 studies, *RAS* WT patients with left-sided tumors had better OS and PFS compared with those with right-sided tumors, irrespective of the treatment received (Table 3, Figure 1). Poor survival was observed in right-sided mCRC patients, and the HRs for OS in both studies demonstrated a worse prognosis for patients with right-sided disease (Supplemental Table 2;

Table 1 Baseline Demographics and Disease Characteristics of *RAS* Wild-type Population

	20050181				20020408			
	Pmab Arm		Comparator Arm		Pmab Arm		Comparator Arm	
Characteristic	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**
Patients	150	31	148	39	42	16	43	14
ECOG PS								
0	78 (52.0)	11 (35.5)	77 (52.0)	19 (48.7)	23 (54.8)	4 (25.0)	12 (27.9)	3 (21.4)
1	66 (44.0)	17 (54.8)	61 (41.2)	17 (43.6)	14 (33.3)	9 (56.3)	22 (51.2)	8 (57.1)
2	6 (4.0)	3 (9.7)	10 (6.8)	3 (7.7)	5 (11.9)	3 (18.8)	9 (20.9)	2 (14.3)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)
Previous adjuvant chemotherapy								
No	115 (76.7)	21 (67.7)	124 (83.8)	32 (82.1)	NA	NA	NA	NA
Yes	31 (20.7)	9 (29.0)	24 (16.2)	6 (15.4)	NA	NA	NA	NA
Sex								
Female	48 (32.0)	15 (48.4)	46 (31.1)	19 (48.7)	18 (42.9)	7 (43.8)	17 (39.5)	4 (28.6)
Male	102 (68.0)	16 (51.6)	102 (68.9)	20 (51.3)	24 (57.1)	9 (56.3)	26 (60.5)	10 (71.4)
***BRAF* status**								
Test failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (2.3)	1 (7.1)
Mutant	7 (4.7)	9 (29.0)	4 (2.7)	13 (33.3)	3 (7.1)	3 (18.8)	2 (4.7)	3 (21.4)
Wild-type	143 (95.3)	22 (71.0)	144 (97.3)	26 (66.7)	39 (92.9)	12 (75.0)	40 (93.0)	10 (71.4)
Metastatic sites								
Liver + other	102 (68.0)	20 (64.5)	90 (60.8)	27 (69.2)	NA	NA	NA	NA
Liver only	29 (19.3)	3 (9.7)	36 (24.3)	5 (12.8)	NA	NA	NA	NA
Other only	19 (12.7)	8 (25.8)	22 (14.9)	7 (17.9)	NA	NA	NA	NA
Age, y								
Median	61	60	60	62	61	55	63	62
Range	28-81	38-77	33-85	42-82	29-78	31-79	32-81	37-78

Data presented as n (%).
Abbreviations: ECOG = Eastern Cooperative Oncology Group; NA = not available; Pmab = panitumumab; PS = performance status.

Table 2 Baseline Demographic Data and Disease Characteristics of *RAS* Mutant Population

	PRIME				PEAK				20050181				20020408			
	Pmab Arm		Comparator Arm		Pmab Arm		Comparator Arm		Pmab Arm		Comparator Arm		Pmab Arm		Comparator Arm	
Characteristic	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**
Patients	166	64	158	70	14	11	19	10	183	76	194	65	61	16	77	21
ECOG PS																
0	89 (53.6)	39 (60.9)	87 (55.1)	36 (51.4)	8 (57.1)	6 (54.5)	9 (47.4)	7 (70.0)	85 (46.4)	43 (56.6)	97 (50.0)	31 (47.7)	31 (50.8)	7 (43.8)	32 (41.6)	5 (23.8)
1	71 (42.8)	20 (31.3)	65 (41.1)	30 (41.1)	6 (42.9)	5 (45.5)	10 (52.6)	3 (30.0)	88 (48.1)	31 (40.8)	84 (43.3)	30 (46.2)	22 (36.1)	6 (37.5)	34 (44.2)	13 (61.9)
2	6 (3.6)	5 (3.6)	6 (3.8)	6 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (5.5)	2 (2.6)	13 (6.7)	3 (4.6)	8 (13.1)	3 (18.8)	11 (14.3)	2 (9.5)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)
Previous adjuvant chemotherapy																
No	139 (83.7)	19 (29.7)	132 (83.5)	69 (98.6)	12 (85.7)	10 (90.9)	15 (78.9)	9 (90.0)	142 (77.6)	56 (73.7)	158 (81.4)	54 (83.1)	NA	NA	NA	NA
Yes	27 (16.3)	45 (70.3)	26 (16.5)	1 (1.4)	2 (14.3)	1 (9.1)	4 (21.1)	1 (10.0)	37 (20.2)	19 (25.0)	35 (18.0)	11 (16.9)	NA	NA	NA	NA
Sex																
Female	59 (35.5)	19 (29.7)	68 (43.0)	28 (40.0)	8 (57.1)	4 (36.4)	8 (42.1)	3 (30.0)	83 (45.4)	32 (42.1)	73 (37.6)	28 (42.1)	28 (45.9)	6 (37.5)	27 (35.1)	21 (100.0)
Male	107 (64.5)	45 (70.3)	90 (57.0)	42 (60.0)	6 (42.9)	7 (63.6)	11 (57.9)	7 (70.0)	100 (54.6)	44 (57.9)	121 (62.4)	37 (56.9)	33 (54.1)	10 (62.5)	50 (64.9)	0 (0.0)
Metastatic sites																
Liver + other	113 (68.1)	49 (76.6)	112 (70.9)	54 (77.1)	4 (28.6)	8 (72.7)	7 (36.8)	6 (60.0)	143 (78.1)	45 (59.2)	85 (46.4)	43 (56.5)	NA	NA	NA	NA
Liver only	31 (18.7)	6 (9.4)	26 (16.5)	10 (14.3)	7 (50.0)	0 (0.0)	3 (15.8)	2 (20.0)	24 (13.1)	14 (18.4)	88 (48.1)	31 (40.8)	NA	NA	NA	NA
Other only	31 (18.7)	9 (14.1)	20 (12.7)	6 (8.6)	3 (21.4)	3 (27.3)	9 (47.4)	2 (20.0)	16 (8.7)	17 (22.4)	10 (5.5)	2 (2.6)	NA	NA	NA	NA
Age, y																
Median	62	66	63	62	59	64	63	65	60	63	64	65	60	64	62	61
Range	35-80	33-83	27-82	33-79	32-78	41-80	39-75	40-72	29-78	35-84	29-86	34-86	27-82	37-77	32-83	27-72

Data presented as n (%).
Abbreviations: ECOG = Eastern Cooperative Oncology Group; NA = not available; Pmab = panitumumab; PS = performance status.

Table 3 Overall Survival, Progression-free Survival, Response Rates, and Duration of Response in *RAS* Wild-type Population

Study	Treatment	Patients		OS, mo; Median (95% CI)		PFS, mo; Median (95% CI)		RR, %; Median (95% CI)		DoR, mo; Median (95% CI)	
		Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
20050181	Pmab + FOLFIRI	150/147[a]	31/30[a]	20.1 (16.5-21.7)	10.3 (5.2-13.7)	8.0 (7.3-9.1)	4.8 (3.5-7.4)	49.7	13.3	7.7 (6.1-9.5)	NE (9.5-NE)
	FOLFIRI	148/144[a]	39/38[a]	16.6 (14.8-21.2)	8.1 (6.3-12.1)	5.8 (5.2-7.3)	2.4 (1.8-5.7)	13.2	2.6	9.3 (5.7-12.3)	NE
	aHR[b]	—	—	0.96 (0.75-1.23)	1.14 (0.68-1.89)	0.88 (0.69-1.12)	0.75 (0.45-1.27)	6.49[c] (3.52-12.26)	5.69[c] (0.51-287.73)	—	—
	P value	—	—	.7388	.6193	.3086	.2859	—	—	—	—
20020408	Pmab + BSC	42/42[a]	16/16[a]	9.4 (7.3-11.7)	3.1 (2.0-12.0)	5.5 (2.6-5.7)	1.7 (1.0-2.8)	23.8	0	5.4 (2.8-12.0)	NA
	BSC	43/43[a]	14/14[a]	8.8 (6.4-10.4)	4.6 (0.9-6.0)	1.6 (1.2-1.8)	1.5 (0.7-1.8)	0	0	—	—
	aHR[d]	—	—	1.02 (0.64-1.63)	0.72 (0.31-1.66)	0.31 (0.19-0.50)	0.50 (0.22-1.15)	Inf[c] (3.51-Inf)	NE	—	—
	P value	—	—	.9326	.4349	<.0001[e]	.1029	—	—	—	—

Abbreviations: aHR = adjusted hazard ratio; BSC = best supportive care; DoR = duration of response; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = folinic acid, 5-fluorouracil, irinotecan; Inf = infinity; NA = not available; NE = not evaluable; OS = overall survival; PFS = progression-free survival; Pmab = panitumumab; RR = response rate.

[a]Number of patients evaluable for response.

[b]Adjusted treatment HR calculated from model with factors for *BRAF* status, previous adjuvant therapy, and baseline ECOG; HR < 1 favors the Pmab arm (study 20050181).

[c]Odds ratio for treatment difference in RR presented; odds ratio > 1 favors the Pmab arm (studies 20050181 and 20020408).

[d]Adjusted treatment HR calculated from model with factors for *BRAF* status and baseline ECOG; HR < 1 favors the Pmab arm (study 20020408).

[e]Statistically significant.

available in the online version). The prognosis remained poor in the *RAS*/*BRAF* WT right-sided population compared with that for those with left-sided tumors, irrespective of the treatment (Supplemental Table 3; available in the online version).

RAS MT. In PEAK, *RAS* MT patients with left-sided tumors had markedly better OS than those with right-sided tumors; however, little to no difference was found in PRIME (Table 4). In the later-line trials (studies 20050181 and 20020408), no clear prognostic difference was evident in the *RAS* MT population. Overall, a prognostic effect of primary tumor location on the HRs for OS was not seen in the *RAS* MT population (Supplemental Table 4; available in the online version).

Predictive Effect of Primary Tumor Location in RAS *WT Patients Undergoing Second- or Later-line Treatment*

The effect of primary tumor location on the outcomes for *RAS* WT patients receiving second- or later-line treatment is shown in Table 3 and Figure 1. In study 20050181, the addition of panitumumab to FOLFIRI resulted in a numerically improved median OS (20.1 vs. 16.6 months; HR, 0.96; $P = .7388$) and PFS (8.0 vs. 5.8 months; HR, 0.88; $P = .3086$) compared with FOLFIRI alone in patients with *RAS* WT left-sided primary tumors. In right-sided mCRC patients, the HR for PFS favored panitumumab (4.8 vs. 2.4 months; HR, 0.75; $P = .2859$), but the HR for OS favored FOLFIRI (10.3 vs. 8.1 months; HR, 1.14; $P = .6193$).

In study 20020408, a significant PFS benefit (5.5 vs. 1.6 months; HR, 0.31; $P < .0001$) was seen when panitumumab was added to BSC for *RAS* WT left-sided mCRC patients. No difference was found in PFS for patients with right-sided tumors (1.7 vs. 1.5 months; HR, 0.50; $P = .1029$). The OS results in that study were difficult to interpret because most patients in the BSC arm crossed over to panitumumab at progression (44 of 57 [77%] of the BSC patients with known tumor side status crossed over to panitumumab).

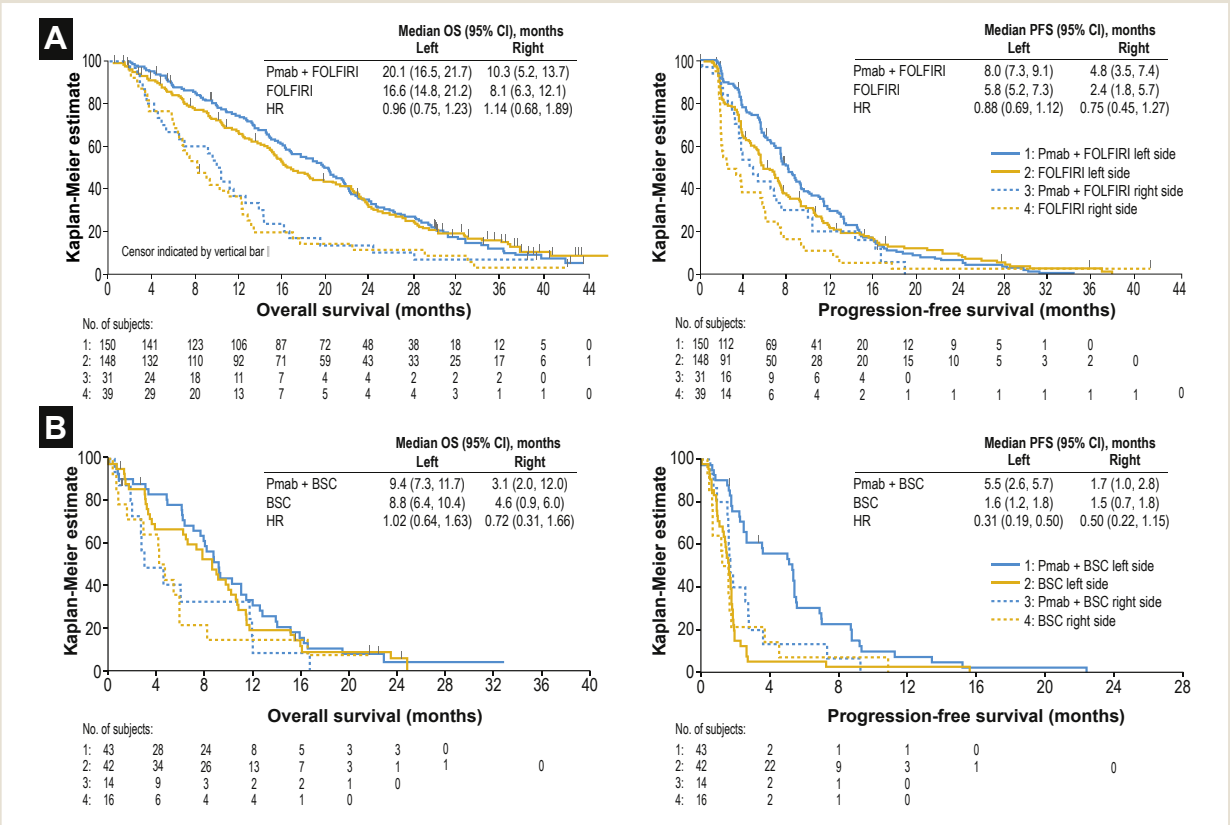
The RRs were greater for the panitumumab versus control arm in the *RAS* WT left-sided mCRC patients in the 20050181 study (50% vs. 13%) and 20020408 study (24% vs. 0%). In patients with right-sided tumors, the same effect was observed in study 20050181 (13% vs. 3%), but no responses were seen in right-sided mCRC in study 20020408, irrespective of treatment. Owing to the low number of responders with right-sided tumors (4 of 30 vs. 1 of 38 evaluable patients in the panitumumab vs. comparator arm in study 20050181 and 0 of 16 vs. 0 of 14 evaluable patients in study 20020408, respectively), no comparison could be made of the DoR stratified by treatment.

The effect of primary tumor location on the outcomes for *RAS*/*BRAF* WT patients receiving second- or later-line treatment is shown in Supplemental Table 3 (available in the online version).

PFS, OS, and RR in RAS *MT Patients*

In PRIME, patients with *RAS* MT left-sided tumors had a significantly worse median PFS in the panitumumab versus FOLFOX arm (7.5 vs. 9.4 months; HR, 1.29; $P = .0288$; Table 4), consistent with the results of the study's primary analysis. The same trend was observed for right-sided mCRC patients (7.4 vs. 8.5 months; HR, 1.37; $P = .0874$). Regarding OS, the HRs favored

Figure 1 Overall Survival (OS) and Progression-free Survival (PFS) in the *RAS* Wild-type Population From the (A) 20050181 and (B) 20020408 Studies



Abbreviations: BSC = best supportive care; CI = confidence interval; FOLFIRI = folinic acid, 5-fluorouracil, irinotecan; HR = hazard ratio; Pmab = panitumumab.

FOLFOX for both left- and right-sided *RAS* MT mCRC patients. No differences between treatments or by location group were observed with respect to RR or DoR.

In PEAK, the results were based on a very small sample size and should therefore be considered with caution. Although left-sided *RAS* MT mCRC patients had worse median PFS in the panitumumab than in the bevacizumab arm (10.2 vs. 12.0 months; HR, 1.29; $P = .4939$), the median OS was markedly longer in the panitumumab arm than in the bevacizumab arm (38.3 vs. 22.9 months; HR, 0.55; $P = .1871$). In right-sided *RAS* MT mCRC, no difference was found in PFS (7.8 vs. 8.7 months; HR, 1.20; $P = .7158$), but the median OS favored panitumumab treatment (19.8 vs. 14.1 months; HR, 0.37; $P = .0765$).

No differences in OS or PFS were observed between treatment arms for left-sided *RAS* MT mCRC patients in the 20050181 study. In patients with right-sided tumors, the panitumumab arm had better OS (14.1 vs. 10.3 months; HR, 0.57; $P = .0027$), although no difference was found in PFS (5.6 vs. 5.3 months; HR, 0.77; $P = .1500$). The median OS appeared to be better in the panitumumab arm in *RAS* MT right-sided mCRC (14.1 months) than left-sided mCRC (11.3 months).

In the 20020408 study, no difference in PFS between treatments in either *RAS* MT tumor location subgroup was observed.

Discussion

To the best of our knowledge, the present study is the first to report the effect of primary tumor location on clinical outcomes during second- or later-line panitumumab treatment. Our results also provide valuable location data for the *RAS* MT cohorts from 4 randomized panitumumab mCRC trials, which have not been explored previously.

Our analyses found prognostic effects in both patients with *RAS* WT and patients with *RAS/BRAF* WT tumors, confirming the prognostic effect of tumor location in second and later treatment lines that was previously reported for the first-line setting.[5,7,14] As was seen in the retrospective analysis of data from the first-line panitumumab studies,[15] *RAS* WT patients with right-sided primary tumors had worse prognosis than those with left-sided tumors in later lines of mCRC treatment. To the best of our knowledge, the present study is the first to demonstrate a prognostic effect beyond first-line treatment in *RAS* WT patients. The observed prognostic effect of tumor location in the second- and later-line *RAS/BRAF* WT population has confirmed that the worse prognosis of right-sided primary tumors does not only result from the presence of *BRAF* mutations, as has been reported previously.[16]

To date, most studies assessing the predictive effect of tumor location on the efficacy of anti-EGFR therapy have focused on cetuximab

Table 4 Overall Survival, Progression-Free Survival, Response Rates, and Duration of Response in *RAS* Mutant Population

Study	Treatment	Patients		OS, mo; Median (95% CI)		PFS, mo; Median (95% CI)		RR, %; Median (95% CI)		DoR, mo; Median (95% CI)	
		Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
PRIME	Pmab + FOLFOX	166/164[a]	64/60[a]	15.8 (13.5-18.4)	15.1 (11.3-19.4)	7.5 (7.1-9.0)	7.4 (6.3-9.0)	44.5	43.3	7.4 (5.7-8.9)	7.4 (5.6-9.2)
	FOLFOX	158/150[a]	70/69[a]	19.7 (16.7-22.4)	16.8 (13.2-24.0)	9.4 (7.7-10.8)	8.5 (5.7-10.4)	44.7	47.8	7.7 (5.6-9.5)	7.7 (5.5-10.9)
	aHR[b]			1.14 (0.90-1.45)	1.36 (0.94-1.98)	1.29 (1.03-1.63)	1.37 (0.96-1.96)	0.99[a] (0.62-1.59)	0.83[a] (0.39-1.77)	—	—
	P value			.2701	.1052	.0288	.0874	—	—	—	—
PEAK	Pmab + FOLFOX	14/14[a]	11/11[a]	38.3 (15.1-53.6)	19.8 (11.8-33.8)	10.2 (5.3-16.6)	7.8 (4.1-10.7)	85.7	45.5	8.5 (3.7-15.1)	5.8 (3.7-7.6)
	Bmab + FOLFOX	19/19[a]	10/10[a]	22.9 (12.6-30.0)	14.1 (3.0-19.4)	12.0 (7.7-14.9)	8.7 (1.7-11.2)	47.4	50.0	6.9 (3.7-24.2)	4.0 (3.8-12.2)
	aHR[c]			0.55 (0.23-1.34)	0.37 (0.12-1.11)	1.29 (0.62-2.70)	1.20 (0.45-3.18)	6.67[d] (0.98-73.07)	0.83[d] (0.11-6.29)	—	—
	P value			.1871	.0765	.4939	.7158	—	—	—	—
20050181	Pmab + FOLFIRI	183/181[a]	76/73[a]	11.3 (9.3-12.5)	14.1 (10.1-16.4)	5.2 (3.8-5.6)	5.6 (3.9-7.9)	14.4	19.2	6.8 (4.2-7.9)	5.6 (3.9-6.5)
	FOLFIRI	195/190[a]	65/60[a]	11.9 (10.4-13.0)	10.3 (7.9-12.5)	5.3 (3.7-5.6)	5.3 (3.4-6.6)	13.2	13.3	5.6 (3.9-8.1)	4.0 (2.7-7.4)
	aHR[e]			1.09 (0.88-1.35)	0.57 (0.40-0.83)	0.96 (0.78-1.18)	0.77 (0.54-1.10)	1.11[d] (0.59-2.09)	1.54[d] (0.55-4.59)	—	—
	P value			.4221	.0027	.6970	.1500	—	—	—	—
20020408	Pmab + BSC	61/61[a]	16/16[a]	5.2 (4.0-6.8)	4.7 (2.1-6.1)	1.7 (1.6-1.8)	1.7 (1.5-1.9)	1.6	0	3.7 (NE)	NA
	BSC	77/77[a]	21/21[a]	5.2 (4.3-7.0)	3.3 (1.3-4.4)	1.8 (1.6-1.8)	1.3 (0.7-1.9)	0	0	NA	NA
	aHR[b]			1.01 (0.70-1.44)	0.63 (0.29-1.37)	1.02 (0.72-1.46)	0.50 (0.23-1.10)	Inf[d] (0.07-Inf)	NE[d]	—	—
	P value			.9739	.2414	.9059	.0862	—	—	—	—

Abbreviations: aHR = adjusted hazard ratio; Bmab = bevacizumab; BSC = best supportive care; DoR = duration of response; ECOG = Eastern Cooperative Oncology Group; Inf = infinity; mCRC = metastatic colorectal cancer; NA = not available; NE = not evaluable; OS = overall survival; PFS = progression-free survival; Pmab = panitumumab; RR = response rate.

[a]Number of patients evaluable for response.

[b]Adjusted treatment HR calculated from model with factors for region and baseline ECOG; HR < 1 favors the Pmab arm (PRIME, 20020408).

[c]Adjusted treatment HR calculated from model with factors for previous adjuvant oxaliplatin therapy; HR < 1 favors the Pmab arm (PEAK).

[d]Odds ratio for treatment difference in RR presented; odds ratio > 1 favors the Pmab arm (PRIME, PEAK, 20050181, 20020408).

[e]Adjusted treatment HR calculated from model with factors for region, baseline ECOG, and previous oxaliplatin exposure for mCRC; HR < 1 favors the Pmab arm (20050181).

data and have yielded results similar to those from the present analyses. In the present report, we found that patients with *RAS* WT left-sided primary tumors benefitted from the addition of panitumumab to chemotherapy or BSC. In the second-line 20050181 study, despite numeric PFS and RR benefits in right-sided *RAS* WT mCRC with the addition of panitumumab, the OS HR appeared to favor FOLFIRI alone (P = NS). Patients with right-sided mCRC undergoing second-line treatment had very low RRs, especially in the FOLFIRI arm. In the 20020408 trial, the addition of panitumumab to BSC resulted in better PFS for patients with left-sided *RAS* WT mCRC, which was also reflected by an improved RR, and once again, the very poor prognosis of right-sided mCRC was confirmed.

Few data have been reported on the effect of primary tumor location in *RAS* MT mCRC. In our analyses, the prognostic effect of tumor location in patients with *RAS* mutations was not clear. Regarding the predictive effect, we found better outcomes favoring the FOLFOX arm in patients with left- and right-sided mCRC in the first-line PRIME trial. These results were not surprising, because they were in line with the study's primary analysis. In the PEAK study, the results should be considered with caution owing to the low number of patients with *RAS* MT tumors (recruitment was limited to patients with *KRAS* exon 2 WT tumors in that study). In patients with left-sided *RAS* MT primary tumors, the median OS in the panitumumab arm was > 50% longer than that seen for bevacizumab; similar results were seen for patients with right-sided primary tumors. These results were unexpected because, although *RAS* MT tumors are known to be resistant to anti-EGFR therapy, this small subgroup of patients did not appear to clearly benefit more from the addition of bevacizumab. These results are consistent with those reported from the first-line CALGB/SWOG (Cancer and Leukemia Group B/Southwestern Oncology Group) 80405 trial[7] and FIRE-3 (FOLFIRI plus cetuximab vs. FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer) trials,[17] in which OS was not significantly different statistically between cetuximab and bevacizumab. In the 20050181 study, the OS for patients with right-sided primary tumors appeared better for the panitumumab arm than for the FOLFIRI arm in *RAS* MT patients. This could be a chance finding, but an alternative hypothesis is whether first-line treatment might induce clonal selection, making some patients more sensitive to anti-EGFR treatment. Validation of these findings in other cohorts is necessary to draw definitive conclusions regarding the optimum treatment of patients with *RAS* MT tumors.

The present study was limited by its retrospective nature and the relatively small number of patients with right-sided primary tumors. Therefore, definitive conclusions could not be drawn regarding the optimum treatment of right-sided mCRC. It would also be useful to assess the effect of biomarkers other than *RAS* and *BRAF*, because these could also affect clinical outcomes. These analyses were, nonetheless, strengthened by the high tumor location and *RAS*/*BRAF* ascertainment rates. The assessors of tumor location were also kept unaware of the *RAS*/*BRAF* mutation status, treatment allocation, and clinical outcomes.

Conclusion

Panitumumab plus chemotherapy or BSC provided better clinical outcomes compared with chemotherapy or BSC alone in *RAS* WT patients with left-sided primary tumors receiving second- or later-line treatment. Because of the relatively small number of patients with right-sided tumors, it was not possible to draw definitive conclusions on the optimal treatment. In view of these and other recently reported findings, tumor location should be considered during treatment decision-making. Further research is needed regarding the optimal treatment of patients with right-sided primary tumors and those with *RAS* MT mCRC.

Clinical Practice Points

- During the past decade, several studies have investigated the clinical effect of primary tumor location in CRC, and it has been reported that patients with right-sided disease have a worse prognosis than patients with left-sided disease.
- Recently, researchers also evaluated the predictive value of tumor location in the treatment of CRC, with most of these studies focusing on data from first-line cetuximab trials.
- In addition, another study from our research group has addressed the effect of primary tumor location on panitumumab treatment in 2 first-line studies.
- We have reported tumor location data from 2 studies of panitumumab after the first treatment line; to the best of our knowledge, ours is the first study to investigate the effect of tumor location in second- and later-line panitumumab studies.
- The results of these analyses have confirmed the negative prognostic effect of right-sided disease in *RAS* WT patients undergoing second- and later-line treatment.
- In addition, we found that patients with *RAS* WT left-sided disease benefit from the addition of panitumumab to chemotherapy or BSC compared with chemotherapy or BSC alone.
- These results are in line with those recently reported from first-line cetuximab and panitumumab studies, showing that patients with left-sided disease benefit from the addition of cetuximab or panitumumab, respectively.
- Our data on right-sided and *RAS* MT disease are inconclusive and require further investigation.
- Nevertheless, it is clear that tumor location is clinically important and should be considered during treatment decision-making.

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Disclosure

R.K. is an employee of Amgen Ltd. C.R. 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. S.S. is a member of advisory boards for Amgen, Bayer, Celgene, Eli Lilly, Merck, Merrimack, Novartis, Roche, and Sanofi. J.T. has had

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Supplemental Data

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References

1. Bufill JA. Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumor location. *Ann Intern Med* 1990; 113:779-88.
2. Lee GH, Malietzis G, Askari A, Bernardo D, Al-Hassi HO, Clark SK. Is right-sided colon cancer different to left-sided colorectal cancer?—A systematic review. *Eur J Surg Oncol* 2015; 41:300-8.
3. Benedix F, Schmidt U, Mroczkowski P, et al. Colon carcinoma—classification into right and left sided cancer or according to colonic subsite? Analysis of 29,568 patients. *Eur J Surg Oncol* 2011; 37:134-9.
4. Brule SY, Jonker DJ, Karapetis CS, et al. Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in NCIC CO.17. *Eur J Cancer* 2015; 51:1405-14.
5. Tejpar S, Stintzing S, Ciardiello F, et al. Prognostic and predictive relevance of primary tumor location in patients with RAS wild-type metastatic colorectal cancer: retrospective analyses of the CRYSTAL and FIRE-3 trials. *JAMA Oncol* 2017; 3:194-201.
6. Arnold D, Lueza B, Douillard JY, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. *Ann Oncol* 2017; 28:1713-29.
7. Venook AP, Niedzwiecki D, Innocenti F, et al. Impact of primary tumor location on overall survival and progression-free survival in patients with metastatic colorectal cancer: analysis of CALGB/SWOG 80405 (Alliance). *J Clin Oncol* 2016; 34(suppl), abstract 3504.
8. Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J Clin Oncol* 2010; 28:4706-13.
9. Peeters M, Oliner KS, Price TJ, et al. Analysis of KRAS/NRAS mutations in a phase III study of panitumumab with FOLFIRI compared with FOLFIRI alone as second-line treatment for metastatic colorectal cancer. *Clin Cancer Res* 2015; 21: 5469-79.
10. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol* 2007; 25:1658-64.
11. Peeters M, Oliner KS, Parker A, et al. Massively parallel tumor multigene sequencing to evaluate response to panitumumab in a randomized phase III study of metastatic colorectal cancer. *Clin Cancer Res* 2013; 19:1902-12.
12. Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med* 2013; 369:1023-34.
13. Rivera F, Karthaus M, Hecht JR, et al. Final analysis of the randomised PEAK trial: overall survival and tumour responses during first-line treatment with mFOLFOX6 plus either panitumumab or bevacizumab in patients with metastatic colorectal carcinoma. *Int J Colorectal Dis* 2017; 32:1179-90.
14. Petrelli F, Tomasello G, Borgonovo K, et al. Prognostic survival associated with left-sided vs right-sided colon cancer: a systematic review and meta-analysis. *JAMA Oncol* 2017; 3:211-9.
15. Boeckx N, Koukakis R, Op de Beeck K, et al. Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer: results from two randomized first-line panitumumab studies. *Ann Oncol* 2017; 28:1862-8.
16. von Einem JC, Heinemann V, von Weikersthal LF, et al. Left-sided primary tumors are associated with favorable prognosis in patients with KRAS codon 12/13 wild-type metastatic colorectal cancer treated with cetuximab plus chemotherapy: an analysis of the AIO KRK-0104 trial. *J Cancer Res Clin Oncol* 2014; 140:1607-14.
17. Stintzing S, Fischer von Weikersthal L, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer-subgroup analysis of patients with KRAS: mutated tumours in the randomised German AIO study KRK-0306. *Ann Oncol* 2012; 23:1693-9.

Supplemental Table 1 General Patient Distribution According to Tumor Location and *RAS* Mutation Status in Different Studies

Variable	First Analysis (*RAS* WT), n (%)						Second Analysis (*RAS* MT), n (%)					
	20050181			20020408			PRIME			PEAK		
	Left	Right	Total	Left	Right	Total	Left	Right	Total	Left	Right	Total
Total population	676 (76.2)	211 (23.8)	887 (100)	223 (76.9)	67 (23.1)	290 (100)	652 (74.6)	222 (25.4)	874 (100)	140 (71.1)	57 (29.4)	197 (100)
RAS WT	298 (81.0)	70 (19.0)	368 (100)	85 (73.9)	30 (26.1)	115 (100)	328 (78.8)	88 (21.2)	416 (100)	107 (74.8)	36 (25.2)	143 (100)
RAS MT	378 (72.8)	141 (27.2)	519 (100)	138 (78.9)	37 (21.1)	175 (100)	324 (70.7)	134 (29.3)	458 (100)	33 (61.1)	21 (38.9)	54 (100)

Abbreviations: MT = mutant; WT = wild-type.

Supplemental Table 2 Overall Survival and Associated Adjusted Hazard Ratios for Patients With Right- Versus Left-sided Tumors (*RAS* Wild-type Population)

Variable	20050181	20020408
Panitumumab arm	Panitumumab + FOLFIRI	Panitumumab + BSC
Median OS (95% CI), mo		
Right-sided	10.3 (5.2-13.7)	3.1 (2.0-12.0)
Left-sided	20.1 (16.5-21.7)	9.4 (7.3-11.7)
aHR[a] (95% CI)	2.01 (1.29-3.13)	1.89 (0.95-3.76)
Comparator arm	FOLFIRI	BSC
Median OS (95% CI), mo		
Right-sided	8.1 (6.3-12.1)	4.6 (0.9-6.0)
Left-sided	16.6 (14.8-21.2)	8.8 (6.4-10.4)
aHR[b] (95% CI)	1.51 (0.96-2.37)	2.41 (1.21-4.81)

Abbreviations: BSC = best supportive care; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; aHR = adjusted hazard ratio; OS = overall survival.
[a]Adjusted treatment HR calculated from a model with factors for *BRAF* status, previous adjuvant therapy, and baseline ECOG (20050181); OS HR > 1 indicates worse prognosis for right-sided tumors.
[b]Adjusted treatment HR calculated from a model with factors for *BRAF* status and baseline ECOG (20020408); OS HR > 1 indicates worse prognosis for right-sided tumors.

Supplemental Table 3 Overall Survival and Progression-free Survival in the *RAS* Wild-type/*BRAF* Wild-type Population

Study	Treatment	Patients, n		OS, mo; Median (95% CI)		PFS, mo; Median (95% CI)	
		Left	Right	Left	Right	Left	Right
20050181	Pmab + FOLFIRI	143	22	19.7 (16.2-21.5)	11.9 (6.4-16.0)	8.0 (7.3-9.1)	6.7 (3.7-10.3)
	FOLFIRI	144	26	17.9 (14.9-23.4)	10.9 (6.7-13.0)	5.8 (5.2-7.3)	3.7 (2.0-5.9)
	aHR[a]	—	—	0.95 (0.70-1.29)	0.84 (0.43-1.62)	0.82 (0.63-1.06)	0.61 (0.31-1.19)
	P value	—	—	.7421	.5937	.1272	.1481
20020408	Pmab + BSC	39	12	9.4 (8.1-12.3)	6.1 (2.0-12.2)	5.5 (2.8-5.7)	1.7 (1.0-3.7)
	BSC	40	10	8.8 (6.4-10.8)	5.2 (0.7-6.0)	1.6 (1.3-1.8)	1.6 (0.5-1.8)
	aHR[b]	—	—	0.87 (0.54-1.40)	0.66 (0.25-1.77)	0.29 (0.18-0.48)	0.54 (0.21-1.39)
	P value	—	—	.5579	.4097	<.0001	.1980

Abbreviations: BSC = best supportive care; ECOG = Eastern Cooperative Oncology Group; aHR = adjusted hazard ratio; mCRC = metastatic colorectal cancer; OS = overall survival; PFS = progression-free survival; Pmab = panitumumab.
[a]Adjusted treatment HR calculated from a model with factors for region, baseline ECOG, and previous oxaliplatin exposure for mCRC (20050181).
[b]Adjusted treatment HR calculated from a model with factors for region and baseline ECOG (20020408).

Supplemental Table 4 Overall Survival and Associated Hazard Ratios for Patients With Right- Versus Left-sided Tumors (*RAS* Mutant Population)

Variable	PRIME	PEAK	20050181	20020408
Panitumumab arm	Panitumumab + FOLFOX	Panitumumab + FOLFOX	Panitumumab + FOLFIRI	Panitumumab + BSC
Median OS, mo				
Right sided	15.1 (11.3-19.4)	38.3 (15.1-53.6)	14.1 (10.1-16.4)	4.7 (2.1-6.1)
Left sided	15.8 (13.5-18.4)	19.8 (11.8-33.8)	11.3 (9.3-12.5)	5.2 (4.0-6.8)
aHR[a,b,c]	1.17 (0.85-1.61)	2.24 (0.87-5.78)	0.84 (0.63-1.11)	1.26 (0.67-2.36)
Comparator arm	FOLFOX	Bevacizumab + FOLFOX	FOLFIRI	BSC
Median OS, mo				
Right sided	16.8 (13.2-24.0)	14.1 (3.0-19.4)	10.3 (7.9-12.5)	3.3 (1.3-4.4)
Left sided	19.7 (16.7-22.4)	22.9 (12.6-30.0)	11.9 (10.4-13.0)	5.2 (4.3-7.0)
aHR[a,b,c]	1.09 (0.81-1.48)	2.8 (1.05-7.43)	1.46 (1.09-1.96)	1.60 (0.95-2.68)

Data in parentheses are 95% confidence interval.
Abbreviations: BSC = best supportive care; ECOG = Eastern Cooperative Oncology Group; aHR = adjusted hazard ratio; mCRC = metastatic colorectal cancer; OS = overall survival.
[a]Adjusted treatment HR calculated from a model with factors for region and baseline ECOG (PRIME, 20020408); OS HR > 1 indicates worse prognosis for right-sided tumors.
[b]Adjusted treatment HR calculated from a model with factors for previous adjuvant oxaliplatin therapy (PEAK); OS HR > 1 indicates worse prognosis for right-sided tumors.
[c]Adjusted treatment HR calculated from a model with factors for region, baseline ECOG, and previous oxaliplatin exposure for mCRC (20050181); OS HR > 1 indicates worse prognosis for right-sided tumors.