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Original article

Understanding the prognostic value of primary tumor location and *KRAS* in metastatic colorectal cancer. A Post-hoc analysis of the OPTIMOX3 DREAM phase III study.

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Running title: Prognostic of primary tumor location and *KRAS* in colorectal cancer

Microabstract: limited to 3-4 sentences (60 words).

This is the first report showing that the better prognosis of mCRC patients with left-sided tumors is driven more strongly by post-progression survival than by progression-free survival when compared with right-sided tumors, whatever KRAS mutation status. This phenomenonwas independent from the exposure to post-study anti-EGFR monoclonal antibody.

ABSTRACT

INTRODUCTION: We evaluated the prognostic value of KRAS and primary tumor location (PTL) for overall survival (OS), progression-free survival (PFS), and post-progression survival (PPS) in metastatic colorectal cancer (mCRC).

MATERIAL AND METHODS: Individual patient data from the DREAM phase III study were retrospectively analyzed. PTL was defined as right-sided or left-sided if tumor arose from the cecum to transverse colon or from the splenic flexure to the rectum, respectively. OS, PFS, and PPS were estimated using the Kaplan-Meier method and compared using log-rank test.

RESULTS: Among 700 patients included in the DREAM study, both PTL and KRAS were available for 536 (76.6%) patients. PTL showed stronger prognostic impact than KRAS status for OS ($HR_{PTL,}$ 1.62 vs. $HR_{KRAS,}$ 1.37), PFS ($HR_{PTL,}$ 1.27 vs. $HR_{KRAS,}$ 1.15) and PPS ($HR_{PTL,}$ 1.54 vs. $HR_{KRAS,}$ 1.33). Interaction between PTL and *KRAS* was significant ($P_{interaction}$ .003). A negative impact of *KRAS* mutation was observed for OS and PPS, but not for PFS. Right-sided tumor was associated with poorer ECOG performance status, anemia, and *KRAS* mutation, while left-sided *KRAS* wild-type tumors with an increased LDH. In patients with *KRAS* mutant mCRC, APL was the main prognostic factor whatever the tumor site, whereas

in those with *KRAS* wild-type tumors prognostic factors varied according to PTL. The exposition to the anti-EGFR agents during and after study was similar in patients with left-sided and right-sided *KRAS* wild-type tumors.

CONCLUSION: Our findings suggest that a better prognosis of mCRC patients with left-sided tumors is driven more strongly by post-progression survival than by PFS when compared with patients with right-sided tumors, whatever *KRAS* mutation status. This phenomenon was independent from the exposition to post-study anti-EGFR monoclonal antibody.

Keywords: colorectal cancer, sidedness, left-sided, right-sided, predictive factor, anti-EGFR, KRAS

INTRODUCTION

About half of the patients with metastatic colorectal cancer (mCRC) harbor a Kirsten rat sarcoma viral oncogene homolog (*KRAS*) or neuroblastoma N-Ras (*NRAS*) tumor gene mutation; both are considered negative predictive biomarkers for anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (MoAbs).[1] Thus, only patients with *KRAS* wild-type mCRC are eligible to EGFR MoAbs.

The DREAM study demonstrated that adding an oral EGFR tyrosine kinase inhibitor to bevacizumab during maintenance therapy improves clinical outcomes (response rate, progression-free survival [PFS] and overall survival [OS]) in patients with mCRC, whatever *KRA*S status.[2] Despite those positive results, erlotinib is not approved for treating patients with advanced CRC. Primary tumor location (PTL) might be a novel predictive marker for the treatment efficacy of EGFR-targeted MoAbs in patients with wild-type *KRAS* mCRC that led to new treatment recommendations.[3-7]

The aim of this study was to evaluate the predictive value of *KRAS* and PTL for OS, PFS, and post-progression survival (PPS) in mCRC.

PATIENTS AND METHODS

Patients and treatment

Individual patient data from the DREAM trial[2] were analyzed. PTL was retrospectively collected and defined right-sided if tumor was located in the cecum to transverse colon and left-sided if primary tumor was located from the splenic flexure to rectum. The *KRAS* tumor gene (exon 2) mutation status was collected from the DREAM study retrospectively between January 2007 and January 2009 and prospectively between January 2009 and October 2011.

Patients were treated with 3 or 6 months bevacizumab and chemotherapy (modified FOLFOX7, modified XELOX, or FOLFIRI) and then randomized, in absence of disease progression, to receive maintenance therapy with bevacizumab alone or bevacizumab plus erlotinib.

Endpoints

Overall survival was defined as the time interval from the date of randomization to death from any cause, or to the last date known to be alive. Progression-free survival was estimated from the date of randomization to the first disease progression (PD) or death from any cause. Patients without documented PD at the cut-off point were censored at their last objective tumor assessment. Patients who died with unknown progression status were censored 4 months after their last tumor evaluation. Post-progression survival was defined as the time interval from the first PD or censoring (no PD) during first-line therapy to death from any cause, or to the last date known to be alive.

Statistical analysis

Bseline comparisons of the demographic, clinical, and mutational characteristics were performed across the groups. OS, PFS, and PPS were estimated using the Kaplan-Meier method and compared using log-rank test. Univariate and multivariate Cox regression analyses were performed to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). The rates were compared using a chi-squared test, or Fisher's exact test if too few events occurred. Analyses were conducted using MedCalc Statistical Software version 16.2.1 (MedCalc Software bvba, Ostend, Belgium).

RESULTS

Patient characteristics

Among 700 patients included in the DREAM study, the KRAS ascertainment rate was 86.8% (n = 608). Tumor location was evaluable in 604 (86.3%) patients (missing data, n = 80; unknown primary site, n = 12; double localization, n = 4; Figure 1).

Of the 536 patients (76.6%) with both PTL and *KRAS* mutation status, 227 (42.4%) had left-sided *KRAS* wild-type tumors, 155 (28.9%) left-sided *KRAS* mutant tumors, 84 (15.7%) right-sided *KRAS* mutant tumors, and 70 (13.0%) right-sided *KRAS* wild-type tumors (Figure 1). The demographic and clinical characteristics are presented in Table 1. Poor Eastern Cooperative Oncology Group performance status (ECOG PS) and anemia were more frequently observed in patients with right-sided tumors than in those with left-sided, whatever the *KRAS* mutation status. An increased level of lactate dehydrogenase (LDH) was more common in patients with left-sided *KRAS* wild-type tumors. The other patient and tumor characteristics were well balanced between four subgroups.

Treatment

In patients with left-sided *KRAS* wild-type tumors, 164 patients (72.2%) received an anti-EGFR therapy that could be on study erlotinib maintenance therapy (n = 90, 39.6%) and/or EGFR MoAb as post-study treatment (n = 125, 55.1%; Supplemental Table 1 in the online version). A total of 55 patients (22.5%) received both erlotinib as maintenance first-line therapy and EGFR MoAb as subsequent line of therapy.

In patients with right-sided *KRAS* wild-type tumors, 48 patients (68.6%) received an anti-EGFR therapy, which could be on study erlotinib maintenance therapy (n = 31, 44.3%) and/or

EGFR MoAb as post-study treatment (n = 30, 42.8%; Supplemental Table 1 in the online version). Thirteen patients (18.6%) received both erlotinib as maintenance first-line therapy and EGFR MoAb as subsequent line of therapy. Thus, the exposition to the EGFR agents was similar in patients with *KRAS* wild-type tumors whatever PTL (*P* = .552) and drug type (erlotinib, *P* = .491; EGFR MoAb, *P* = .074).

KRAS

A negative impact of *KRAS* mutation was observed on OS and PPS, but not on PFS (Figure 2). The median OS were 30.2 months (95% CI, 27.5-32.3) and 22.7 months (95% CI, 21.3-25.5) for patients with *KRAS* wild-type and mutant tumors, respectively (HR 1.37; 95% CI, 1.13-1.65; *P* < .001). The median PFS was 9.7 months (95% CI, 8.9-10.5) and months 9.2 (95% CI, 8.1-10.1) for patients with *KRAS* wild-type and mutant tumors, respectively (HR 1.15; 95% CI, 0.96-1.38; *P* = .120). The median PPS was 17.5 months (95% CI, 13.8-19.7) and 13.0 months (95% CI, 10.9-15.6) in patients with *KRAS* wild-type and mutant tumors, respectively (HR 1.33; 95% CI, 1.10-1.60; *P* = 0.002).

Primary Tumor Location

Left colon versus rectal tumors

Of the 429 patients with left-sided tumors, 265 (61.8%) had left colon cancer and 164 (38.2%) rectal cancer. When excluding 47 patients (10.9%) with missing data for *KRAS*, a *KRAS* mutation was observed in 93 (38.8%) and 62 (43.7%) patients with left colon and rectal tumors, respectively (*P* = .048). The median OS were 29.4 months (95% CI, 25.0-32.8) and 28.0 months (95% CI, 24.2-31.5) for patients with left colon and rectal tumors, respectively (HR 1.09; 95% CI, 0.88-1.38; *P* = .425 ; Figure 2). The median PFS was 9.8 months (95% CI,

8.9-10.8) and 9.6 months (95% CI, 8.5-10.8) for patients with left colon and rectal tumors, respectively (HR 1.02; 95% CI, 0.83-1.27; *P* = .811; Figure 2). Based on these results, left colon and rectal tumors were merged into one group, left-sided CRCs, for further analysis.

Left-sided CRC versus right-sided colon tumors

KRAS mutation was less common in patients with left-sided tumors (n = 155, 40.6%) than in those with right-sided tumors (n = 84, 54.5%; *P* < .001). The median OS was 28.8 months (95% CI, 25.4-31.4) and 19.5 months (95% CI, 16.5-21.3) for patients with left-sided and right-sided tumors, respectively (HR 1.62; 95% CI, 1.29-2.01). The median PFS was 9.7 months (95% CI, 8.9-10.5) and 8.3 months (95% CI, 7.7-9.4) for patients with left-sided and right-sided tumors, respectively (HR 1.27; 95% CI, 1.03-1.56). The median PPS was 16.1 months (95% CI, 13.4-17.9) and 9.8 months (95% CI, 7.4-12.2) for patients with left-sided and right-sided tumors, respectively (HR 1.54; 95% CI, 1.24-1.91; *P* < 0.001).

KRAS and Primary Tumor Location

There was no difference between the analyzed (N=536) and excluded (N=164) populations in terms of PFS and PPS, but there was a slight difference in terms of OS in favor of analyzed patients in terms of OS (HR 0.82 ; 95% CI 0.66-1.01, P = .048)

Interaction

Interaction between PTL and *KRAS* was significant ($P_{interaction}$ = .003).

OS

In patients with *KRAS* wild-type tumors, the median OS was 32.3 months (95% CI, 29.5-35.5) and 20.3 months (95% CI, 18.0-27.5) for left-sided and right-sided tumors, respectively (HR

1.52; 95% CI, 1.10-2.10; Table 2). OS did not differ between patients who received and those who did not receive EGFR MoAb as post-study treatment, whatever PTL (left-sided *KRAS* wild-type, HR_{OS} 0.94; 95% CI, 0.68-1.30, P = .731; right-sided *KRAS* wild-type, HR_{OS} 1.27; 95% CI, 0.74-2.18, P = .365; Supplemental Table 2 in the online version).

In patients with *KRAS* mutant tumors, the median OS was 24.9 months (95% CI, 22.5-30.0) and 19.4 months (95% CI, 15.8-22.0) for left-sided and right-sided tumors, respectively (HR 1.56; 95% CI, 1.10-2.21; Figure 3).

PFS

In patients with *KRAS* wild-type tumors, the median PFS was 9.9 months (95% CI, 8.9-10.8) and 9.4 months (95% CI, 8.1-11.0) for left-sided and right-sided tumors, respectively (HR 1.07; 95% CI, 0.80-1.45; Table 2).

In patients with *KRAS* mutant tumors, the median PFS was 9.9 months (95% CI, 8.6-11.3) and 7.9 months (95% CI, 6.8-9.6) for left-sided and right-sided tumors, respectively (HR 1.45; 95% CI, 1.05-2.00; Figure 3).

PPS

In patients with *KRAS* wild-type tumors, the median PPS was 18.7 months (95% CI, 14.5-22.3) and 12.1 months (95% CI, 8.7-14.3) for left-sided and right-sided tumors, respectively (HR 1.50; 95% CI, 1.06-2.13; P = .008, Table 2).

In patients with *KRAS* mutant tumors, the median PPS was 15.4 months (95% CI, 12.6-17.6) and 9.8 months (95% CI, 6.4-13.4) for left-sided and right-sided tumors, respectively (HR 1.44; 95% CI, 1.05-1.97; P = .013; Figure 3).

Prognostic factors

Prognostic factors for OS vary according to PTL and *KRAS* status.

In univariate analysis, three variables, white blood cell count (WBC), LDH, and alkaline phosphatase (APL), were ubiquitarious prognostic factors across four subgroups according to PTL and *KRAS* (Table 3). Hemoglobin level was a prognostic factor for patients with *KRAS* wild-type tumors, whatever PTL. ECOG PS and the number of metastatic sites were prognostic factors only in patients with left-sided *KRAS* wild-type tumors.

In multivariate analysis, APL, the number of metastatic sites, ECOG PS, and LDH level were independent prognostic factors for OS in patients with left-sided *KRAS* wild-type tumors, while WBC and LDH level in those with right-sided *KRAS* wild-type tumors (Table 4). In left-sided *KRAS* mutant tumors, APL and LDH level were two independent prognostic factors for OS, and in those with right-sided *KRAS* mutant tumors, APL was the only independent prognostic factor.

DISCUSSION

The prognostic value of PTL was stronger than *KRAS* status in mCRC for OS ($HR_{PTL,}$ 1.62 vs. $HR_{KRAS,}$ 1.37), PFS ($HR_{PTL,}$ 1.27 vs. $HR_{KRAS,}$ 1.15) and PPS ($HR_{PTL,}$ 1.54 vs. $HR_{KRAS,}$ 1.33).

The poor prognostic value of right-sided tumors was in the same range that previously observed in first-line studies.[1,8,9] In our study, right-sided tumors were associated with poorer ECOG PS, anemia, and *KRAS* mutation, while left-sided *KRAS* wild-type tumors were associated with an increased level of LDH.

Our data show that *KRAS* mutation was slightly more frequent in rectal tumors than in left colon, but similar results for PFS and OS were observed between these two cancer groups in agreement with previous reports.[10] Nevertheless, it could be helpful to keep subgrouping

based on different molecular profiles (e.g., *HER2* genetic alterations in rectal tumors, *PI3KCA* mutation in left-colon cancers) for the future therapeutic management and further targeted trials.[11]

In patients with *KRAS* mutant tumors, APL was the main prognostic factor whatever the tumor site, whereas prognostic factors vary according to PTL in patients with *KRAS* wild-type tumors (APL, the number of sites, ECOG PS, and LDH in left-sided *KRAS* wild-type tumors, and WBC and LDH in right-sided *KRAS* wild-type tumors). Thus, general prognostic models for OS should not be applied to clinical dataset without weighted rules according to PTL and *KRAS* status in patients with mCRC.

Interestingly, the prognostic impact of PTL and *KRAS* is more pronounced after progression than during the first-line treatment period. In our study, this phenomenon was independent of the EGFR treatment effect. Indeed, the exposition to the EGFR agents was similar in left-sided and right-sided tumors and there was no difference between these two tumor groups in terms of clinical outcomes (OS, PPS) regardless of whatever patients received anti-EGFR MoAb or did not receive after study treatment.

This post-hoc analysis has inherent limitations, although the data ascertainment of PTL was high (89%). Other shortcomings of this study are the restriction of *KRAS* mutation analysis to only exon 2, lack of analysis of the “rare mutations” status at other locations of *KRAS*, *NRAS*, and *BRAF* tumors genes, as well as the limited number of patients in each subgroup. *BRAF* and *NRAS* mutations are present in roughly 10% and 4% of advanced CRC, respectively, but are overrepresented in right-sided *KRAS* wild-type tumors. This work will be proposed to the ARCAD Advanced Colorectal Cancer database program for further analysis based on extended molecular profile, including *KRAS*, *NRAS* and *BRAF* genes.[12]

CONCLUSION

Good prognosis of mCRC patients with left-sided tumors is driven more strongly by post-progression survival than by PFS when compared to patients with right-sided tumors, whatever *KRAS* mutation status. This phenomenon was independent of the exposition to post-study anti-EGFR MoAb.

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REFERENCES

1. Lièvre A, Bachet JB, Le Corre D, et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Res* 2006; 66:3992-5.
2. Tournigand C, Chibaudel B, Samson B, et al. Bevacizumab with or without erlotinib as maintenance therapy in patients with metastatic colorectal cancer (GERCOR DREAM; OPTIMOX3): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2015; 16:1493-1505.
3. 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.
4. Venook AP, Niedzwiecki D, Innocenti F et al. Impact of primary (1º) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance). *J of Clin Oncol* 2018; 34:3504.
5. Holch JW, Ricard I, Stintzing S, et al. The relevance of primary tumour location in patients with metastatic colorectal cancer: A meta-analysis of first-line clinical trials. *Eur J Cancer* 2017; 70:87-98.
6. 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; 28:1862-68.
7. 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.

8. Loupakis F, Yang D, Yau, et al. Primary tumor location as a prognostic factor in metastatic colorectal cancer. *J Natl Cancer Inst* 2015; 107(3).
9. Schrag D, Weng S, Brooks G, et al. The relationship between primary tumor sidedness and prognosis in colorectal cancer. *J of Clin Oncol* 2016; 34 (15_suppl; abstr 3505).
10. Salem ME, Yin J, Weinberg BA, et al. Clinicopathological differences and survival outcomes with first-line therapy in patients with left-sided colon cancer and rectal cancer: Pooled analysis of 2879 patients from AGITG (MAX), COIN, FOCUS2, OPUS, CRYSTAL and COIN-B trials in the ARCAD database. *Eur J Cancer* 2018; 103:205-13.
11. Seo AN, Kwak Y, Kim DW, et al. HER2 status in colorectal cancer: its clinical significance and the relationship between HER2 gene amplification and expression. *PLoS One* 2014; 9:e98528.
12. Buyse M, Sargent DJ, Goldberg RM, et al. The ARCAD advanced colorectal cancer database--open for business. *Ann Oncol* 2012; 23:281-2.

Table 1. Patient characteristics according to *KRAS* mutation status and primary tumor location (n = 536)

Abbreviations: WT, wild-type; Mut, mutant; ECOG PS, Eastern Cooperative Oncology Group performance status; BMI, body mass index; WBC, white blood cells; LDH; lactate hydrogenase; ALP, alkaline phosphatase; CEA, carcinoembryonic antigen; ULN, upper limit of normal; MoAb, monoclonal antibody; EGFR, epidermal growth factor receptor

Table 2. Summary of clinical outcomes.

Abbreviations: OS, overall survival; PFS, progression-free survival; PPS, post-progression survival

Table 3. Univariate analysis of prognostic factors for overall survival according to post-progression survival and *KRAS* mutation status

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; BMI, body mass index; WBC, white blood cells; LDH; lactate hydrogenase; ALP, alkaline phosphatase; CEA, carcinoembryonic antigen; ULN, upper limit of normal

Table 4. Multivariate analysis of prognostic factors for overall survival according to primary tumor location and *KRAS* mutation status

Abbreviations: HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; WBC, white blood cell; LDH, lactate dehydrogenase; APL, alkaline phosphatase

Figure 1. Flow diagram (n = 700)

Abbreviations: WT, wild-type; PTL, primary tumor location

Figure 2. Overall survival (A), progression-free survival (B), and post-progression survival (C) according to primary tumor location and *KRAS* mutation status

Figure 3. Median progression-free survival and post-progression survival according to primary tumor location and *KRAS* mutation status

Abbreviations: WT, wild-type; Mut, mutant

Table 1.

	Left-sided *KRAS* wild-type n (%)	**Right-sided *KRAS* wild-type** n (%)	**Left-sided *KRAS* mutant** n (%)t	**Right-sided *KRAS* mutant** n (%)	*P* value
Total no. of patients	227	70	155	84	
Age					.159
< 70	177 (78.0)	49 (70.0)	106 (68.4)	64 (76.2)	
≥ 70	50 (22.0)	21 (30.0)	49 (31.6)	20 (23.8)	
Gender					.570
Male	140 (61.7)	48 (68.6)	91 (58.7)	51 (60.7)	
Female	87 (38.3)	22 (31.4)	64 (41.3)	33 (39.3)	
ECOG PS					.037
0	132 (58.1)	34 (48.6)	98 (63.2)	38 (45.2)	
1	83 (36.6)	35 (50.0)	50 (32.3)	43 (51.2)	
2	12 (5.3)	1 (1.4)	7 (4.5)	3 (3.6)	
BMI					.605
< 30	192 (84.6)	61 (87.1)	125 (80.6)	71 (84.5)	
≥ 30	35 (15.4)	9 (12.9)	30 (19.4)	13 (15.5)	
Time to metastasis					.283
Metachronous	36 (15.9)	8 (11.4)	25 (16.1)	7 (8.3)	
Synchronous	191 (84.1)	62 (88.6)	130 (83.9)	77 (91.7)	
No. of metastatic sites					.998
1	111 (48.9)	34 (48.6)	77 (49.7)	41 (48.8)	
> 1	116 (51.1)	36 (51.4)	78 (50.3)	43 (51.2)	
WBC					.668
< 10,000	193 (85.0)	60 (85.7)	126 (81.3)	68 (81.0)	
≥ 10,000	34 (15.0)	10 (14.3)	29 (18.7)	16 (19.0)	
Hemoglobin					<.001
(g/dL)	155 (68.9)	36 (52.2)	103 (67.8)	38 (45.2)	
> 12	70 (31.1)	33 (47.8)	49 (32.2)	46 (54.8)	
< 12					
LDH					.015
≤ 1 x ULN	84 (37.3)	35 (50.0)	76 (49.4)	45 (54.9)	
> 1 x ULN	141 (62.7)	35 (50.0)	78 (50.6)	37 (45.1)	
ALP					.401
< 3 x ULN	201 (88.9)	64 (91.4)	145 (93.5)	74 (88.1)	
≥ 3 x ULN	25 (11.1)	6 (8.6)	10 (6.5)	10 (11.9)	

CEA					.425
< 5 x ULN	80 (36.5)	33 (48.5)	57 (38.3)	33 (41.2)	
5-100 x ULN	97 (44.3)	24 (35.3)	60 (40.3)	37 (46.2)	
> 100 x ULN	42 (19.2)	11 (16.2)	32 (21.5)	10 (12.5)	
EGFR therapy					
No	63	22	110	59	WT, *P* = .552
Yes	164 (72.2)	48 (68.6)	45 (29.0)	25 (29.8)	Mut, *P* = .906
Erlotinib (on study)	90 (39.6)	31 (44.3)	45 (29.0)	23 (27.4)	
EGFR MoAb (post-study)	125 (55.1)	30 (42.8)	1 (0.6)	2 (2.4)	

Table 2.

	KRAS wild-type		*KRAS* mutant	
	Left-sided	Right-sided	Left-sided	Right-sided
Total, n	227	70	155	84
OS, months (median, 95% CI)	32.3 (29.5-35.5)	20.3 (18.0-27.5)	24.9 (22.5-30.0)	19.4 (15.8-22.0)
	HR 1.52 (1.10-2.10)		HR 1.56 (1.10-2.21)	
PFS, months (median, 95% CI)	9.9 (8.9-10.8)	9.4 (8.1-11.0)	9.9 (8.6-11.3)	7.9 (6.8-9.6)
	HR 1.07 (0.80-1.45)		HR 1.45 (1.05-2.00)	
PPS, months (median, 95% CI)	18.7 (14.5-22.3)	12.1 (8.7-14.3)	15.4 (12.6-17.6)	9.8 (6.4-13.4)
	HR 1.50 (1.06-2.13)		HR 1.44 (1.15-1.97)	

Table 3.

	Left-sided *KRAS* wild-type		Right-sided *KRAS* wild-type		Left-sided *KRAS* mutant		Right-sided *KRAS* mutant	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (< 70 vs. ≥ 70)	1.20 (0.81-1.79)	.332	0.97 (0.53-1.76)	.931	0.95 (0.64-1.39)	.778	0.96 (0.56-1.65)	.893
Gender (male vs. female)	0.88 (0.64-1.21)	.430	1.24 (0.68-2.26)	.456	0.93 (0.64-1.35)	.711	0.93 (0.58-1.48)	.752
ECOG PS (0 vs. 1-2)	1.77 (1.26-2.49)	< .001	1.52 (0.88-2.61)	.112	1.27 (0.85-1.88)	.221	1.18 (0.74-1.88)	.477
BMI (< 30 vs. ≥ 30)	0.70 (0.47-1.04)	.115	0.61 (0.31-1.20)	.213	0.76 (0.50-1.16)	.235	0.66 (0.37-1.17)	.210
Metachronous vs. synchronous	1.29 (0.87-1.93)	.242	1.49 (0.67-3.27)	.393	1.29 (0.81-2.05)	.318	1.96 (0.98-3.91)	.130
No. of metastatic sites (1 vs. > 1)	1.48 (1.08-2.03)	.014	0.97 (0.57-1.66)	.914	1.09 (0.76-1.58)	.631	1.96 (0.98-3.91)	.130
WBC (< 10,000 vs. ≥ 10,000)	1.66 (0.99-	.016	3.36 (1.05-	< .001	1.49 (0.88-	.083	1.84 (0.93-	.025

	2.75)		10.68)		2.51)		3.64)	
Hemoglobin (> 12 vs. < 12)	1.94 (1.32-2.84)	< .001	2.19 (1.25-3.84)	.002	0.94 (0.63-1.41)	.777	0.99 (0.63-1.59)	.994
LDH (≤ 1 x ULN vs. > 1 x ULN)	1.56 (1.14-2.15)	.008	2.46 (1.41-4.29)	< .001	2.01 (1.38-2.93)	.0001	1.71 (1.04-2.79)	.019
APL (< 3 x ULN vs. ≥ 3 x ULN)	2.92 (1.50-5.71)	< .001	4.36 (0.73-25.95)	< .001	6.63 (1.29-34.05)	< .001	3.73 (1.17-11.87)	< .001
CEA (< 10 x ULN vs. > 10 x ULN)	1.26 (0.91-1.75)	.155	1.20 (0.68-2.10)	.510	1.32 (0.91-1.92)	.146	1.41 (0.85-2.35)	.154

Table 4.

Variables	HR	95% CI	*P* value
Left-sided *KRAS* wild-type			
ECOG PS	1.45	1.03-2.04	.035
No. of metastatic sites	1.84	1.30-2.60	< .001
WBC	1.28	0.81-2.01	.287
Hemoglobin	1.49	1.04-2.13	.030
LDH	1.22	0.85-1.77	.280
APL	2.76	1.66-4.61	< .001
Right-sided *KRAS* wild-type			
WBC	2.60	1.09-6.18	.031
Hemoglobin	1.75	0.94-3.24	.076
LDH	2.44	1.28-4.63	.006
APL	2.98	0.85-10.37	.086
Left-sided *KRAS* mutant			
WBC	1.50	0.94-2.41	.089

LDH	1.90	1.29-2.82	.001
APL	5.41	2.49-11.80	< .001
Right-sided *KRAS* mutant			
WBC	1.20	0.61-2.35	.592
LDH	1.46	0.83-2.55	.189
APL	3.01	1.40-6.44	.005

Figure 1.

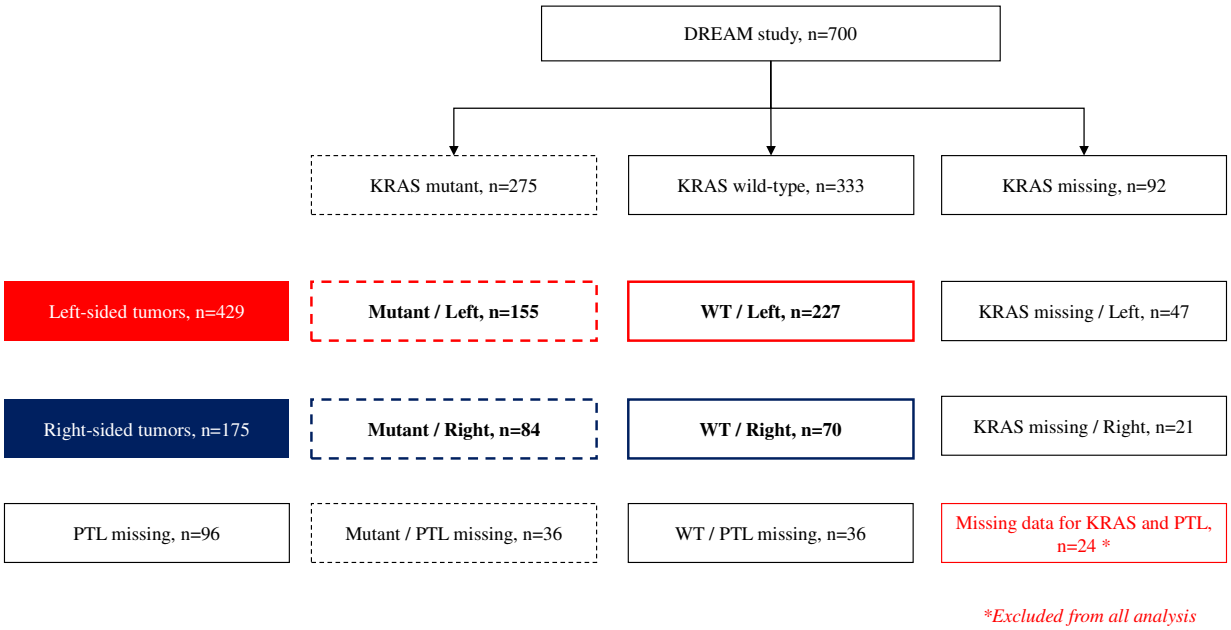
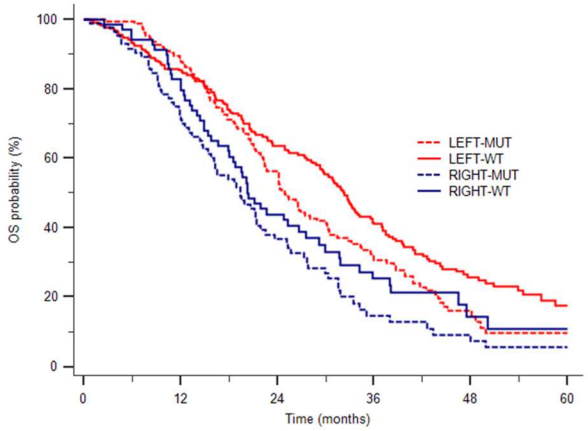
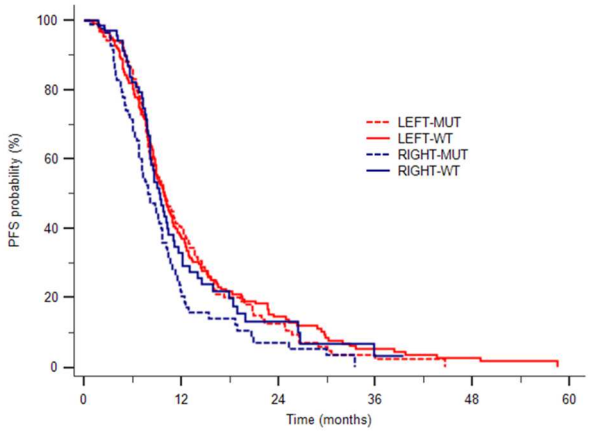

DREAM study, n=700
KRAS mutant, n=275
KRAS wild-type, n=333
KRAS missing, n=92
Left-sided tumors, n=429
Mutant / Left, n=155
WT / Left, n=227
KRAS missing / Left, n=47
Right-sided tumors, n=175
Mutant / Right, n=84
WT / Right, n=70
KRAS missing / Right, n=21
PTL missing, n=96
Mutant / PTL missing, n=36
WT / PTL missing, n=36
Missing data for KRAS and PTL, n=24 *
*Excluded from all analysis

Figure 2.

A


OS probability (%)
100
80
60
40
20
0
0
12
24
36
48
60
Time (months)
LEFT-MUT
LEFT-WT
RIGHT-MUT
RIGHT-WT

B


PFS probability (%)
100
80
60
40
20
0
0
12
24
36
48
60
Time (months)
LEFT-MUT
LEFT-WT
RIGHT-MUT
RIGHT-WT

C

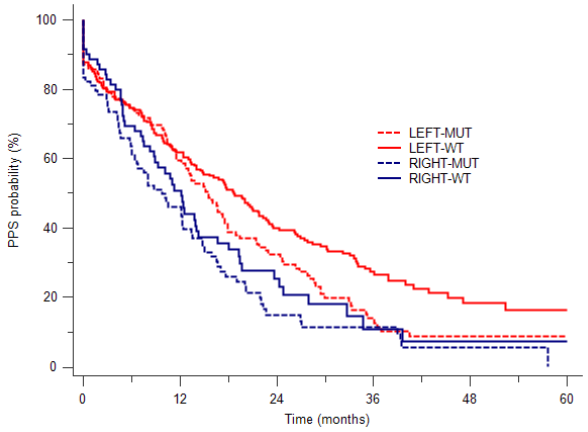
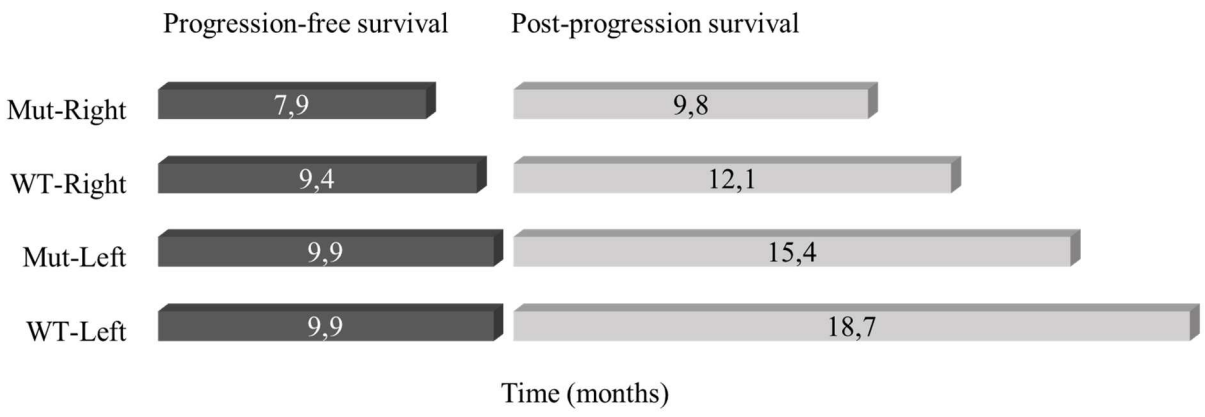

PPS probability (%)
100
80
60
40
20
0
0
12
24
36
48
60
Time (months)
LEFT-MUT
LEFT-WT
RIGHT-MUT
RIGHT-WT

Figure 3.


Progression-free survival
Post-progression survival
Mut-Right
7,9
9,8
WT-Right
9,4
12,1
Mut-Left
9,9
15,4
WT-Left
9,9
18,7
Time (months)